SPECIAL REPORT

Serum Infliximab Concentrations in Psoriatic Patients Treated with Infliximab: A Systematic Review

Carole DANNEPOND[1,2], Annabel MARUANI[1–3], Laurent MACHET[1–3], David TERNANT[1,4], Gilles PAINTAUD[1,4] and Mahtab SAMIMI[1,2,5]

[1]University Hospital of Tours, University François Rabelais, [2]Dermatology Department, Hospital of Tours, [3]Inserm, Imagerie et Cerveau UMR U930, [4]CNRS, GICC UMR 7292, Laboratory of Pharmacology Toxicology, Hospital of Tours, and [5]Laboratory of Molecular Virology and Immunology, ISP 1282 INRA-University François Rabelais, Tours, France

The efficacy of infliximab is influenced by individual variability in its pharmacokinetics and pharmacodynamics. Serum infliximab concentrations could therefore be related to the efficacy and tolerance of infliximab, and assist adjustment of treatment. The aim of this systematic review was to assess the value of measuring serum infliximab concentrations in psoriatic patients. A bibliographic search was performed on MEDLINE, CENTRAL, EMBASE, LILACS for original studies on serum infliximab concentrations in psoriatic patients treated with infliximab. Ten articles were included, representing evaluation of serum infliximab concentrations in 733 patients. Predictive value of higher serum infliximab concentrations on long-term response maintenance was suggested in 3 studies. There was no information regarding the value of such measurements for adjustment of infliximab dosage. Trough serum infliximab concentrations that are at least detectable (>0.1 mg/l) at steady state (week 22) seem to be associated with maintaining a clinical response in the long term. *Key words: infliximab; psoriasis; pharmacokinetics; trough concentration.*

Mahtab Samimi, Department of Dermatology, Laboratory of Molecular Virology and Immunology, ISP 1282, INRA-University François Rabelais, Hospital of Tours, FR-37000 Tours, France. E-mail: samimi.mahtab@yahoo.fr

Infliximab (IFX) is a chimeric monoclonal antibody directed against tumour necrosis factor alpha (TNFα) that is approved for treatment of cutaneous psoriasis, with a recommended dosage schedule of 5 mg/kg/infusion intravenously at weeks 0, 2, 6 and subsequently every 8 weeks. Variable efficacy of IFX in psoriatic patients has been reported (1–3), leading to individual dose adjustments by shortening intervals between infusions and/or dose increase in non-responsive patients (4, 5). These between-patient response differences reflect intra- and inter-individual variability of IFX pharmacokinetics and pharmacodynamics in psoriatic patients, as in other inflammatory diseases. This can be investigated by evaluating the IFX concentration levels in patients' blood samples just after (peak concentration) and just before (trough concentration) IFX infusions. Serum IFX concentrations in inflammatory rheumatic and bowel diseases have been reported to be related to IFX efficacy (6–14), to be valuable in guiding individual dose adjustment (12, 15–19), to constitute a predictive marker of long-term response to treatment (8, 20–25) and to be a marker of antibodies against infliximab (ATI) (6, 9, 10, 13, 26–29). In such diseases, monitoring of serum IFX concentrations has been recommended in clinical practice in cases of primary inadequate response, secondary loss of response, and in cases of hypersensitivity reactions and autoimmune diseases (8, 16).

There is currently no information on the validity and value of measurement of IFX concentrations in psoriatic patients. We therefore undertook a systematic review of published reports on patients treated with IFX for cutaneous psoriasis and for whom serum IFX concentration had been measured. Our aims were: 1) to report the technical procedures used for such measurement, 2) to describe IFX pharmacokinetics in psoriatic patients, 3) to assess the relationship between serum IFX concentration and IFX efficacy, 4) to assess any association between serum IFX concentration and ATI, 5) to assess any association between serum IFX concentration and the occurrence of adverse side effects, and 6) to investigate whether serum IFX concentrations may be used to guide IFX dose adjustment in order to optimise treatment.

MATERIALS AND METHODS

The PRISMA guidelines were followed for the systematic review.

Search strategy

One author (CD) undertook a systematic search on January 20, 2013 of the electronic databases MEDLINE, CENTRAL, EMBASE, LILACS, with no limitation on date or language, to identify articles about infliximab and psoriasis. No methodological search filters or limits were applied. The keywords "psoriasis" and "infliximab" associated with "AND" were used in a simple MEDLINE search, and with keywords in "title and abstract" in EMBASE, CENTRAL and LILACS.

Inclusion and exclusion criteria

The inclusion criteria were defined as: any original article (study, case series, item of correspondence) reporting measurement of serum IFX concentrations for at least 2 patients treated with IFX for cutaneous psoriasis. The exclusion criteria were defined as: reviews and guidelines, editorials, articles on IFX-induced psoriasis or psoriatic arthritis, and single case reports. Reviews and guidelines mentioning "infliximab concentration", "infliximab levels", or "infliximab pharmacokinetics" were excluded from the selection, but their references were analysed by one author (CD) to extend the research.

Study selection strategy

According to the pre-defined criteria, first-line selection based on titles was performed by one author (CD). Second-line selection based on abstracts was performed independently by 2 authors (CD, MS). Discordant selections were discussed. Full texts of the subsequently selected articles were examined independently by 2 authors (CD, MS). Duplicate publications were identified by several criteria (authors, title, intervention characteristics, and number of patients).

Data extraction

The extraction table was developed by 3 authors (CD, MS, AM). The extraction itself was performed independently by 2 authors (CD, MS), and discordance was resolved after discussion. The data collected included the general characteristics of the article (author, title, publication date, study design, key outcomes), patient characteristics (sample size, gender, type of psoriasis), IFX treatment regimen (duration, dosage and adjustments, combination with other systemic drugs), measurement of serum IFX concentrations (technical procedures, time and results of assays, pharmacokinetics), IFX efficiency (clinical scores) and side effects (presence of ATI, occurrence of adverse effects), and authors' recommendations on the value of measuring IFX serum concentration.

Data analysis

Descriptive continuous variables were reported as medians and ranges, mean and standard deviations, and percentages.

RESULTS

Literature search and characteristics of articles included in the study

The flowchart of the literature search is presented in Fig. S1[1]. After exclusion of inter-database duplicates, 3,733 articles were identified. Selection based on titles included 2,179 articles and selection based on abstracts identified 229 for full text analysis. Overall, 10 articles (3, 26–34) (Table I) met our inclusion criteria and were eligible for data extraction. Eight were original articles (4 randomised clinical trials (3, 26–28), 3 prospective open studies (29–31) and one observational study (32)). Two additional articles (33, 34) were duplicate publications of selected studies, but were retained in the analysis because they provided additional data on assessment of serum IFX concentrations. Population characteristics, infliximab regimen, methods and times of serum IFX concentration assays are summarised in Table I and Table SI[1]. The studies involved 1,677 patients, most of whom had plaque psoriasis. IFX dosages ranged between 3 and 10 mg/kg, and the drug was administered at weeks 0, 2, 6 and then every 8 weeks. Patients had IFX dosage adjustments in one study (32).

Table I. *Overview of the 10 included articles: study design and population characteristics*

First author, year	Type of study (duration)	Focus on serum infliximab concentration?	N/N$_I$	Men (%)	Age, years Mean ± SD [range]	Type of psoriasis
Gottlieb, et al., 200) (26)	Monocentre, prospective, randomised, double-blind study (W0–W14)	No, secondary outcome (subgroup analysis)	33/17	69.7	43.7 ± 14.1	Plaque
Reich, et al., 2005 (3)	Multicentre, prospective, randomised, double-blind study (W0–W50)	No, secondary outcome (subgroup analysis)	378/169	71.0	42.8 ± 11.9	Plaque
Menter, et al., 2007 (27)	Multicentre, prospective, randomised, double-blind study (W0–W50)	No, secondary outcome (subgroup analysis)	835/178	66.4	44.1 ± 12.7	Plaque
Zhu, et al., *2006 (33)*	*Duplicate of Menter (27)*	*Yes, primary outcome (subgroup analysis)*	*835/178*	*66.4*	*44.1 ± 12.7*	*Plaque*
Torii & Nakagawa, 2010 (28)	Multicentre, prospective, randomised, double-blind study (W0–W14) followed by an open study (W14–W78)	No, secondary outcome (all patients)	54/54	62.9	46.9 ± 13.0	Plaque
Torii & Nakagawa 2011 (29)	Multicentre, prospective open study (W0–W50)	No, secondary outcome (all patients)	65/65	64.1	46.3 ± 13.3	Plaque, pustular, erythrodermic
Torii, et al., *2012 (34)*	*Retrospective analysis of 2 previous studies (Torii 2010 and 2011)*	*Yes, primary outcome (subgroup analysis)*	*114/90*	*64.0*	*46.5 ± 12.9*	*Plaque, pustular, erythrodermic*
Takahashi, et al., 2012 (30)	Monocentre, prospective, open study (W0–W48)	Yes, main outcome (subgroup analysis)	52/20	58.0	57.5 [47.0–72.0]	Plaque, pustular
Gottlieb, et al., 2012 (31)	Multicentre, prospective, open study (W0–W26)	No, secondary outcome (all patients)	215/215	63.7	44.4 ± 13.3	Plaque
Meyer, et al., 2012 (32)	Monocentre, observational study	Yes, primary outcome (subgroup analysis)	45/15	73.0	Median = 50.0 Ranges = 22.0–80.0	Plaque

Gender and age were reported for all patients included (data not available for subgroups of patients for whom serum infliximab concentration was measured). W: week; N: number of patients included in the study; N$_I$: number of patients with measurements of serum infliximab concentration; SD: standard deviation. (In italic: duplicate publications).

Measurement of IFX concentrations: techniques and pharmacokinetics

Serum IFX concentrations had been measured in 733 patients (43.7%). Measurements were performed by enzyme-linked immunosorbent assay (ELISA) for 334 patients (45.5%) and radioimmunoassay (RIA) for 15 patients (2.1%). The measurement technique was not mentioned for 384 patients (52.4%). Sampling methods, delivery times and storage of samples were available in 2 studies ($n = 37$ patients) (26, 30) The lowest limit of detection of the ELISA technique was 0.1 mg/l in 4 studies ($n = 314$ patients) (26–29) and 0.05 mg/l in one study (30) ($n = 20$ patients). Inter- and intra-assay variability was detailed in one study using RIA (<20% and <10%) (32). Serum IFX concentration was measured before infusion (trough serum infliximab, TSI) in 8 studies ($n = 733$ patients) and one hour after infusion (peak concentration) in 4 studies ($n = 305$ patients). The pharmacokinetics of TSI are reported in Table II. In the short term (W0, W2, W6 and W14) (5 studies, 520 patients) (3, 26, 28, 29, 31), maximum TSI were obtained at W2, and then gradually decreased until W14. Data after W22 were available in 5 studies (681 patients) (3, 27–29, 31) and showed that TSI reached a steady state at W22, maintained until W70, ranging between 0.1 and 3.7 mg/l. The relationship between IFX dose and serum concentration was assessed by Gottlieb et al. (26) (5 mg/kg vs 10 mg/kg) and Menter et al. (27) (3 mg/kg vs 5 mg/kg). The IFX serum peak at W2 was proportional to the dose (26). TSI at W14 was dose-dependent but not proportional (26). Similarly, TSI at steady state (W22) was 2.6 mg/l in the 5 mg/kg group but undetectable in the 3 mg/kg group (27). The pharmacokinetics of IFX were similar for different clinical subtypes of psoriasis (1 study, 65 patients) (29).

In the same study, 14 patients had systemic treatment combined with IFX (methotrexate, oral corticosteroids) but without information on their influence on the IFX pharmacokinetics or on the development of ATI (29).

Relationship between trough serum infliximab levels (TSI) and IFX efficacy

A positive relationship between TSI and clinical efficacy (PASI75 or PASI90) assessed at the same time was reported in 4 studies (89 patients) (28, 30, 32, 34). Long-term responders (over 18 months) had detectable TSI (32). PASI75 increased gradually with TSI (PASI75 response rates at W62 being 60%, 71.4% and 95.7% for TSI lower than 0.1 mg/l, between 0.1 and 1 mg/l and between 1 and 10 mg/l, respectively) (28). TSI over 0.9 mg/l at W48 was associated with increased PASI75 response (30). TSI at W54 was higher in PASI90 responders (median 2.6 mg/l, interquartile range 1.1 to 3.8 mg/l) than in non-responders (median 0.1 mg/l, interquartile <0.1–1.4 mg/l) (34). In the study by Menter et al. comparing different IFX dosages (3 mg/kg versus 5 mg/kg) (27), the relationship between IFX efficacy and TSI varied when considering the induction or the maintenance phase of IFX treatment. No relationship was evidenced at the induction phase, as both IFX dosages resulted in similar efficacy, whereas median TSI was lower in the 3 mg/kg (6.2 μg/ml) than in the 5 mg/kg (23.5 μg/ml) group. On the other hand, PASI75 responses were better achieved in the 5 mg/kg group (with detectable TSI), compared to the 3 mg/kg group (with undetectable TSI). A positive relationship between TSI assessed at one time and clinical efficacy at subsequent times, reflecting a predictive value, was reported in 3 studies (437 patients) (3, 33, 34). Reich et al. (3) reported that PASI75 responders at W50 had

Table II. *Pharmacokinetics of infliximab: evolution of trough serum infliximab over time*

First author, year	Dosage (mg/kg)	Trough serum infliximab (mg/l), in median (ranges)[a]				
		W2[b]	W14	W22	W30	W46
Gottlieb, et al., 2003 (26)	5.0	30.0 (6.0–60.0)	0.7 (NA–5.0)	Not available	Not available	Not available
	10.0	60.0 (15.0–130.0)	7.1 (4.0–20.0)	Not available	Not available	Not available
Reich, et al., 2005 (3)	5.0	Not available	Not available	Concentration of IFX stabilised from W22 to W46 2.8–3.7		
Menter, et al., 2007 (27)	3.0	Not available	Not available	<0.1	<0.1	<0.1
	5.0	Not available	Not available	2.6	1.6	2.1
Zhu, et al., *2006 (33)*	*3.0*	*Not available*	*Not available*	*<0.1*	*<0.1*	*<0.1*
	5.0			*2.6*	*1.6*	*2.1*
Torii & Nakagawa 2010 (28)	5.0	25.0	2.4	2.0	1.5	2.2
Torii, et al., 2011 (29)	5.0	20.0	2.5–5.0	0.8–2.5	0.7–2.5	0.1–2.0
Torii, et al., *2012 (34)*	*5.0*	*25.0*	*2.2*	*2.0*	*1.7*	*1.5*
Takahashi, et al., 2012 (30)	Mean = 4.6 Ranges = 4.1–5.2	Not available	Not available	Not available	Not available	Not available
Gottlieb, et al., 2012 (31)	5.0	35.1	4.3	2.8	Not available	Not available
Meyer, et al., 2012 (32)	Median = 5.1 Ranges = 4.6–6.5	Not available	Not available	Not available	Not available	Not available

[a]Serum infliximab concentrations are reported as expressed in the studies, i.e in median (with ranges), median with no ranges, or ranges of medians (« between … and… »).

W: week. (In italic: duplicate publications).

had TSI over 1 mg/l at steady state (W22), compared to levels under 1 mg/l at W22 and undetectable from W30 to W50 for non-responders. Similarly, Torii et al. (34) reported that PASI 90 responders at W46 had had TSI above 2 mg/l at steady state compared to levels under 1 mg/l at W30 and 0.1 mg/l at W46 for non-responders. Another study stated that the proportion of responders was associated with TSI, with no additional information (33).

Relationship between serum IFX concentrations, IFX antibody (ATI) detection and adverse events

Detection of ATI was reported to be associated with «low» (30, 31) or undetectable (28) TSI with no additional data. Among 15 patients who had detectable TSI, none had ATI (32). No study assessed whether serum IFX concentrations were predictive of the development of ATI. No information was available on any relationship between serum IFX concentrations and the occurrence of adverse side effects.

Value of serum IFX concentrations for adjustment of dosage of IFX

No study had assessed the value of measurement of serum IFX concentration for dosage adjustment in psoriatic patients.

According to the authors of the studies included, measurement of serum IFX concentrations may predict effectiveness and maintenance of the clinical response (3, 27, 30).

DISCUSSION

We undertook the first systematic review assessing the validity and value of measurement of serum IFX concentrations in the management of patients treated with IFX for cutaneous psoriasis.

Measurement of serum IFX concentrations: techniques and pharmacokinetics

Serum IFX concentrations were mostly measured before infusion (trough serum infliximab levels, TSI) over the time of treatment with IFX at the usual dosage (5 mg/kg/8 weeks) for plaque psoriasis. The ELISA technique, the technique that was most commonly used, is limited by the threshold of detection and the interference with the detection of ATI (35). RIA, a more sensitive assay (36), was rarely used because it is less widely available. When available, sampling methods, sample management and techniques of measurement were neither homogeneous nor standardised, making it difficult to define reproducible thresholds between different laboratories. However, pharmacokinetics data

showed that TSI reached steady state after 4 infusions (W22), the median TSI ranging from 0.8 mg/l to 3.7 mg/l with no long-term drug accumulation (3, 27–29, 31). Inter-individual variability in the elimination half-life and TSI make it difficult to predict individual pharmacokinetics (3, 26). The clinical subtype of psoriasis did not appear to affect the pharmacokinetics (29), but no data were available on the effects of individual factors previously reported to influence infliximab pharmacokinetics, such as gender, weight, albumin serum concentration, degree of systemic inflammation, and combination with other drugs including methotrexate (37).

Relationship between trough serum infliximab levels and IFX efficacy

A positive relationship between TSI and clinical efficacy assessed at the same time was reported in 4 studies (28, 30, 32, 34), in agreement with studies on rheumatoid arthritis (11–14) and inflammatory bowel disease (6–10). This review also points out the interesting positive relationship between higher TSI at steady state (W22) and the long-term maintenance of clinical efficacy in psoriasis (3, 34). The threshold of TSI predictive of response maintenance cannot however be clearly defined, the range in these studies being "detectable" (> 0.1 mg/l) (27), to 1 mg/l (3) or 2 mg/l (34). Such a predictive threshold has also been reported in rheumatoid arthritis and Crohn's disease, for similar thresholds (20–25). Undetectable TSI might be associated with an increased risk of further loss of response to IFX. However, it is not known whether this reflects inadequate exposure to IFX and thus whether these patients may benefit from dose adjustment of infliximab (3). In rheumatoid arthritis and Crohn's disease, TSI assessment has been reported to help the clinician with infliximab management in non-responder patients. Indeed, a low TSI would justify dose escalation whereas a high TSI would lead to infliximab withdrawal and change to another drug (12, 15–17, 19). However, we found no studies evaluating such a strategy or the value of TSI for individual IFX dosage adjustment in psoriatic patients.

Relationship between serum IFX concentrations, ATI detection and adverse events

Low TSI in non-responsive patients may also reflect development of ATI. Indeed, ATI increases the clearance of infliximab and decreases its efficacy (35). It has been shown in inflammatory rheumatism that low TSI levels were predictive of ATI development, suggesting that monitoring of TSI might detect underexposed patients at risk of immunisation (38). In our review, some authors indicated that TSI levels at

steady state were lower or undetectable in the case of ATI (3, 28, 30) but no further details were available in these reports. It is not known whether low TSI levels could predict ATI development in psoriatic patients, and no study had evaluated whether dosage adjustments based on TSI monitoring would reduce risk of immunisation. Similarly, no information was available on a relationship between TSI and the occurrence of adverse side effects.

Limitations and conclusions

This systematic review is limited by the number of available studies with only 2 papers investigating the evaluation of serum IFX concentrations as a main outcome (30, 32). Serum IFX concentrations were measured using varying technical procedures and the results were often incompletely reported, and/or were for subgroups of patients or limited periods of time. At least detectable TSI levels (> 0.1 mg/l) at steady state (W22) seem to be associated with maintaining a clinical response in the long term. Measurement of serum IFX concentrations could therefore identify patients at risk of loss of clinical response, but further studies are needed to assess whether additional strategies (dose adjustment, combination with methotrexate) would help maintain long term effective response to IFX in these patients. Overall, no study had as its aim the clinical value of long-term TSI monitoring, especially in dose adjustment strategies, and this remains to be evaluated in prospective studies.

REFERENCES

1. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet 2001; 357: 1842–1847.
2. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004; 51: 534–542.
3. Reich K, Nestle FO, Papp K, Ortonne J-P, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 2005; 366: 1367–1374.
4. Luber AJ, Tsui CL, Heinecke GM, Lebwohl MG, Levitt JO. Long-term durability and dose escalation patterns in infliximab therapy for psoriasis. J Am Acad Dermatol 2014; 70: 525–532.
5. Mehren CR, Gniadecki R. Dose-creep of Infliximab during psoriasis treatment: an observational study. Acta Derm

Venereol 2012; 92: 355–357.
6. Levesque BG, Greenberg GR, Zou G, Sandborn WJ, Singh S, Hauenstein S, et al. A prospective cohort study to determine the relationship between serum infliximab concentration and efficacy in patients with luminal Crohn's disease. Aliment Pharmacol Ther 2014; 39: 1126–1135.
7. Adedokun OJ, Xu Z, Padgett L, Blank M, Johanns J, Griffiths A, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. Inflamm Bowel Dis 2013; 19: 2753–2762.
8. Eser A, Primas C, Reinisch W. Drug monitoring of biologics in inflammatory bowel disease. Curr Opin Gastroenterol 2013; 29: 391–396.
9. Marits P, Landucci L, Sundin U, Davidsdottir L, Nilsson J, Befrits R, et al. Trough s-infliximab and antibodies towards infliximab in a cohort of 79 IBD patients with maintenance infliximab treatment. J Crohns Colitis 2014; 8: 881–889.
10. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OØ, Ainsworth MA. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol 2011; 46: 310–318.
11. Wolbink GJ, Voskuyl AE, Lems WF, de Groot E, Nurmohamed MT, Tak PP, et al. Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis 2005; 64: 704–707.
12. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002; 46: 1451–1459.
13. Radstake TRDJ, Svenson M, Eijsbouts AM, van den Hoogen FHJ, Enevold C, van Riel PLCM, et al. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 2009; 68: 1739–1745.
14. Takeuchi T, Miyasaka N, Inoue K, Abe T, Koike T. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol Jpn Rheum Assoc 2009; 19: 478–487.
15. Mulleman D, Méric J-C, Paintaud G, Ducourau E, Magdelaine-Beuzelin C, Valat J-P, et al. Infliximab concentration monitoring improves the control of disease activity in rheumatoid arthritis. Arthritis Res Ther 2009; 11: R178.
16. Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010; 105: 1133–1139.
17. Rahman MU, Strusberg I, Geusens P, Berman A, Yocum D, Baker D, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis 2007; 66: 1233–1238.
18. Hibi T, Sakuraba A, Watanabe M, Motoya S, Ito H, Motegi K, et al. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn's disease. Inflamm Bowel Dis 2012; 18: 1480–1487.
19. Van der Maas A, van den Bemt BJF, Wolbink G, van den Hoogen FHJ, van Riel PLCM, den Broeder AA. Low infliximab serum trough levels and anti-infliximab antibodies are prevalent in rheumatoid arthritis patients treated with infliximab in daily clinical practice: results of an observatio-

nal cohort study. BMC Musculoskelet Disord 2012; 13: 184.

20. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014; 63: 1721–1727.

21. Van den Bemt BJF, den Broeder AA, Wolbink G-J, van den Maas A, Hekster YA, van Riel PLCM, et al. The combined use of disease activity and infliximab serum trough concentrations for early prediction of (non-)response to infliximab in rheumatoid arthritis. Br J Clin Pharmacol 2013; 76: 939–945.

22. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. Gut 2010; 59: 49–54.

23. Mulleman D, Chu Miow Lin D, Ducourau E, Emond P, Ternant D, Magdelaine-Beuzelin C, et al. Trough infliximab concentrations predict efficacy and sustained control of disease activity in rheumatoid arthritis. Ther Drug Monit 2010; 32: 232–236.

24. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2006; 4: 1248–1254.

25. Chu Miow Lin D, Mulleman D, Azzopardi N, Griffoul-Espitalier I, Valat J-P, Paintaud G, et al. Trough infliximab concentration may predict long-term maintenance of infliximab in ankylosing spondylitis. Scand J Rheumatol 2010; 39: 97–98.

26. Gottlieb AB, Masud S, Ramamurthi R, Abdulghani A, Romano P, Chaudhari U, et al. Pharmacodynamic and pharmacokinetic response to anti-tumor necrosis factor-alpha monoclonal antibody (infliximab) treatment of moderate to severe psoriasis vulgaris. J Am Acad Dermatol 2003; 48: 68–75.

27. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007; 56: 31.e1–15.

28. 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: 40–49.

29. Torii H, Nakagawa H, Japanese Infliximab Study Investigators. Long-term study of infliximab in Japanese patients with plaque psoriasis, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma. J Dermatol 2011; 38: 321–334.

30. Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H. Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis. J Dermatol 2013; 40: 39–42.

31. Gottlieb AB, Kalb RE, Blauvelt A, Heffernan MP, Sofen HL, Ferris LK, 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: 642–650.

32. Meyer MW, Zachariae C, Bendtzen K, Skov L. Lack of anti-drug antibodies in patients with psoriasis well-controlled on long-term treatment with tumour necrosis factor inhibitors. Acta Derm Venereol 2012; 92: 362–364.

33. Zhu Y, Menter A, Jang H, Zhou H. Pharmacokinetics and pharmacodynamics of infliximab in a phase III trial in patients with plaque-type psoriasis. J Am Acad Dermatol 2006; 54: AB222.

34. Torii H, Sato N, Yoshinari T, Nakagawa H, Japanese Infliximab Study Investigators. Dramatic impact of a Psoriasis Area and Severity Index 90 response on the quality of life in patients with psoriasis: an analysis of Japanese clinical trials of infliximab. J Dermatol 2012; 39: 253–259.

35. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013; 72: 1947–1955.

36. Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatol Oxf Engl 2007; 46: 1828–1834.

37. Ternant D, Paintaud G. Pharmacokinetics and concentration-effect relationships of therapeutic monoclonal antibodies and fusion proteins. Expert Opin Biol Ther 2005; 5 Suppl 1: S37–47.