Detection of Infliximab and Anti-Infliximab Antibodies with ELISA or High-Performance Liquid Chromatography (Reference — 2013.03.009)

Notice of Assessment

April 2014

1 GENERAL INFORMATION

1.1 Requestor

- Hôpital Maisonneuve Rosemont (HMR)
- Hôpital Saint-Luc du CHUM

1.2 Application for Review Submitted to MSSS

- HMR: July 24, 2013
- Hôpital Saint-Luc du CHUM: September 28, 2013

1.3 Application Received by INESSS

November 1, 2013

1.4 Notice Issued

February 28, 2014

Note:
This notice is based on the scientific and commercial information submitted by the requestors and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology

ELISA (enzyme-linked immunosorbent assay) with quantitative results for infliximab (IFX), and semi-quantitative results for detection of anti-IFX antibodies.

Quantitative measurement by high-performance liquid chromatography (HPLC) using homogeneous mobility shift assay (HMSA) to detect IFX and anti-IFX antibodies.

2.2 Brief Description of the Technologies, and Clinical and Technical Specifications

Two separate tests are used to assess the efficacy of IFX treatment: determination of IFX and of anti-IFX antibody serum levels. The requestors have proposed two different technical approaches.

2.2.1 ELISA

The Promonitor®-IFX kit (Proteomika S. L., subsidiary of Progenika Biopharma S.A., Spain) is used for quantitative determination of serum IFX levels in a sample. This is an ELISA assay (on a solid substrate) that uses an antibody to allow free IFX in serum to hybridize to tumour necrosis factor alpha (TNFα) fixed on the solid substrate (microwells). Quantification is performed after hybridization of a second monoclonal antibody, coupled to HRP enzyme and directed against the IFX portion of IFX/TNFα complexes fixed to the substrate. An enzyme reaction using a chromogen (TMB[5]) then allows quantification of the number of TNFα/IFX complexes by assessing the intensity of the colorimetric reaction by spectrophotometry and use of a calibration curve. The signal obtained is proportional to the amount of IFX in the patient sample.

[5] TMB: 3,3',5,5'-tetramethylbenzidine.

Figure 1: Illustration of immunoenzymatic complexes formed during ELISA assay

Source: http://www.proteomika.com/index.php?option=com_content&task=view&lang=en&id=318&Itemid=293. Figure reproduced with permission from Progenika Biopharma S.A.

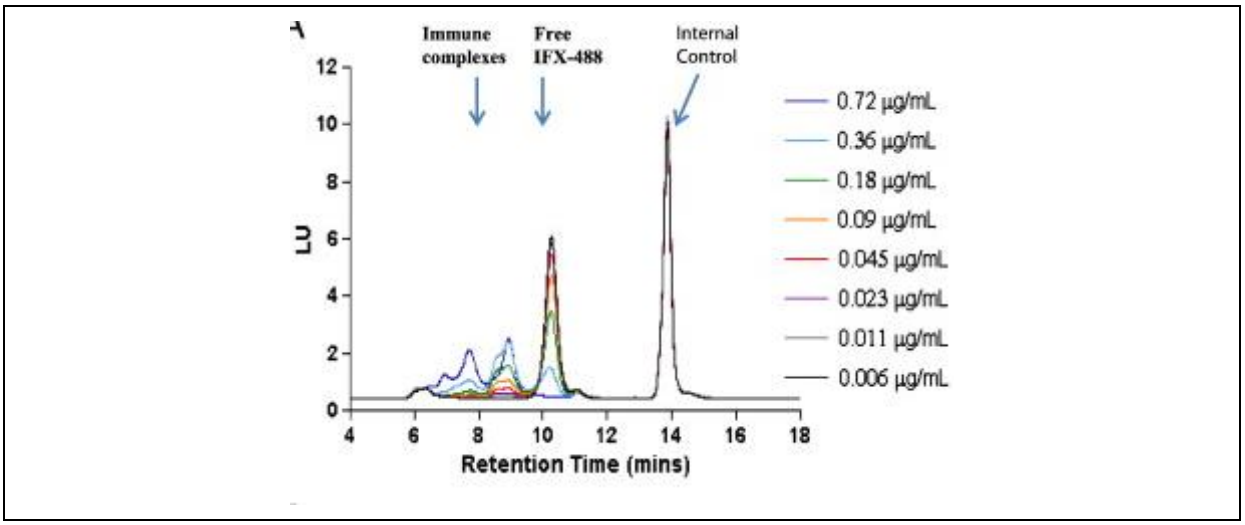
The Promonitor®-anti-IFX kit is used for semi-quantitative determination of anti-IFX antibodies. This ELISA assay quantifies anti-IFX antibody levels. The procedure is similar to the previous one, except the signal obtained is proportional to the amount of antibodies directed against IFX in the patient sample.

For reasons of efficiency, these assays will be automated on the DSX System from Dynex Magellan Biosciences (analytical platform for automation of ELISA immunoassays).
An external control program will be implemented at the beginning of 2014.

2.2.2 HPLC-HMSA

Both assays use this technique with a similar approach. The assay uses IFX (for quantification of anti-IFX) or TNFα (for quantification of IFX) molecules coupled with Alexa fluor 488. Depending on the assay chosen, one molecule or the other is incubated with the serum of patients undergoing treatment. Formation and quantification of TNFα-488/IFX or IFX-488/anti-IFX complexes is then assessed by HPLC. The complexes formed appear as late peaks compared with the peak from the substrate alone. Calculation of proportions of IFX or TNFα that are free versus captured as complexes allows for quantification of IFX or anti-IFX antibodies.

Figure 2: HPLC electrophoresis resolution profile illustrating retention time for anti-IFX/IFX-488 complexes versus free IFX-488



Source: adapted from Wang et al., 2012. Figure reproduced with the author's permission.

Wang et al. [2012] report that their procedure, which includes a step for acid dissociation of IFX and anti-IFX potentially present in patient serum, reduces interference and allows the test to be performed without regard for time of last dose taken, unlike ELISA assays that are subject to interference from free IFX. Free IFX could cause a cross-reaction that would prevent optimal detection of anti-IFX.

According to the requestor, there is no external control program for this test.

2.3 Company or Developer

The ELISA method was described by Engvall and Perlmann [1971]. Several ELISA kits are available for this test.

The HPLC-HMSA method was described by Wang et al. [2012].

2.4 Licence(s)

Not applicable (ELISA and HPLC-HMSA).

2.5 Patent, If Any

ELISA: Not applicable.
HPLC-HMSA: the method described by Wang et al. [2012] is probably similar to that used by Prometheus Therapeutics and Diagnostics (United States) for the Anser®-IFX test. This company has filed a patent for the test.

2.6 Approval Status (Health Canada, FDA)

ELISA: the assay does not use kits approved by Health Canada. The kits are approved by the European Union (CE Mark).

HPLC-HMSA: uses the Alexa Fluor kit from Invitrogen (Frederick, CA), which serves as a fluorochrome for several antibodies already approved by Health Canada.

2.7 Weighted Value

ELISA: 155.10 (estimated in 2013).
HPLC-HMSA: 65.33 (estimated in 2013).

3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patient Group

IFX is an exceptional medication in Quebec, specifically indicated for the following moderate to severe diseases: Crohn disease, rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic spondylitis. It is also indicated for a severe form of chronic plaque psoriasis [RAMQ, 2013]. Target patients for the assays under review have primary or secondary resistance or suboptimal response to IFX. In fact, 30% of patients do not respond to anti-TNFα therapy. Additionally, secondary resistance develops in 20% to 60% of those who present a primary response [Nanda et al., 2013; Wang et al., 2012].

3.2 Targeted Disease(s)

Crohn disease is an idiopathic inflammatory disease of the intestine that may involve the entire gastrointestinal tract [Peppercorn, 2013]. Clinical manifestations are variable and may include fatigue, prolonged diarrhea with abdominal pain, weight loss, fever, and proctorrhagia. The disease is characterized by intermittent exacerbations followed by periods of remission [Peppercorn, 2013]. A study of the epidemiology of Crohn disease in Quebec reported an age- and sex-standardized prevalence of 189.7 cases per 100,000 people between 1993 and 2002, and an age- and sex-standardized incidence of 20.2 cases/100,000 person-years for the period 1998–2000 [Lowe, 2009].

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily affects joints. Although it may be remitting, RA can lead to joint destruction and deformity if not controlled. In patients who do not respond to treatment, significant disability may occur within 10 to 20 years after diagnosis [Venables and Maini, 2012]. RA has a significant effect on patient functional capacity and quality of life, and it is associated with increased mortality [Tarride et al., 2013; Venables and Maini, 2013]. The prevalence of RA in Canada is around 1% of the population [Tarride et al., 2013; Arthritis Alliance of Canada, 2011; Badley and Desmeules, 2003].

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease characterized by pain, joint stiffness, and progressive loss of spinal mobility than can lead to severe functional limitations [Kobelt et al., 2006]. There is a correlation between the prevalence of the HLA-B27 antigen and the prevalence of AS [Yu, 2012]. It is difficult to estimate prevalence and incidence, and they vary based on community and region (for example, prevalence ranging from 1.1% to 7.5% is reported in various communities in the US, and incidence can vary from 1.5 per 100,000 to 10 per 100,000 person-years in different European countries) [Yu, 2012].

Psoriasis is a chronic systemic, inflammatory auto-immune disease that affects approximately 1 million Canadians. Roughly one-third are considered moderate to severe cases [Wasel et al., 2009]. Psoriasis can have a significant effect on quality of life, it is associated with an increased risk of comorbidities (e.g., obesity, type 2 diabetes), and it has negative social, financial, and psychological consequences [Wasel et al., 2009].

Tumour necrosis factor-alpha (TNFα) plays a central role in the pathogenesis of these diseases [Kopylov et al., 2012; Suryaprasad and Prindiville, 2003]. Protein molecules that block TNFα, such as IFX (a human-murine chimeric monoclonal antibody), are effective at reducing inflammatory disease activity [Tracey et al., 2008]. However, in many cases, there is a loss of response; the reason for this is not always understood, although formation of anti-IFX antibodies seems to play an important role. Formation of these antibodies primarily directed against the murine portion of IFX is reported by up to 60% of patients. The antibodies may appear with the initial dose and can persist up to 4.5 years after therapy is discontinued. The antibodies have been reported to neutralize the drug or increase its clearance. Some studies associate low IFX levels with a loss of clinical response, diminished quality of life, and increased health care costs.

3.3 Number of Patients Targeted

According to RAMQ data, the number of patients treated with infliximab in Quebec increased from 98 in 2002 to 2,992 in 2013. No fewer than 80 of these cases (< 3%) are pediatric (age 17 and under). Of the total number, 58% of patients had Crohn disease, 18% had RA, 10% had AS, and 8% had psoriasis. The diagnosis was unknown for the remaining 6%. Considering the average annual increase noted in the number of patients taking infliximab over the last three years (10.2%), and assuming that no new indications are added for this treatment, the expected number of patients taking this drug would be 3,297 in 2014, 3,633 in 2015, and 4,004 in 2016. According to the requestor, the expected number of tests in Quebec would be approximately 280 per year.

A review of 16 studies on Crohn disease, involving 2,236 patients representing 6,284 years of follow-up, estimated that 37% of patients had a loss of IFX response during the treatment period observed and the risk for loss of IFX response was 13% per patient-year [Gisbert and Panés, 2009]. The percentage of patients treated with infliximab who are tested varies from centre to centre; overall, 20% of patients are tested each year.[6] This would mean 598 assays in 2013. However, this percentage could increase if the test is entered in the Index. According to information provided by MSSS, 236 tests were sent to Prometheus Therapeutics and Diagnostics between April 1, 2012, and December 31, 2013.[7]

3.4 Medical Specialties and Other Professions Involved

Rheumatologists, dermatologists, gastroenterologists, immunologists.

3.5 Testing Procedure

Collection is performed at the hospital, by venipuncture.

[6] Personal communication with Dr. Raymond Lahaie (Hôpital Saint-Luc du CHUM); January 13, 2014.
[7] Information provided by MSSS, Quebec, November 12, 2013.

4 TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology

Assays that would replace tests sent outside Quebec.

4.2 Brief Description of the Current Technological Context

Test and clinical (disease activity) results are used to determine the efficacy of IFX treatment, predict treatment-related reactions, and determine clinical loss of response to treatment.

Tests are currently performed outside Quebec.

4.3 Brief Description of the Advantages Cited for the New Technology

Drug-related side effects, lack of primary response, and secondary drug resistance are frequent problems with anti-TNFα agents, and compromise treatment optimization [Martin du Pain et al., 2009]. These problems have significant repercussions for patient health and result in additional costs for the health care system. The proposed tests would improve treatment (e.g., by increasing the dose or changing medication) and clinical management of the target diseases, reduce use of other health care services (e.g., visits to emergency departments, hospitalizations, physician visits) and improve the cost-effectiveness of treatment [Adisen et al., 2010; Afif et al., 2010].

Although the clinical usefulness and relative performance advantage of ELISA versus HPLC-HMSA have not been clearly shown, HPLC-HMSA has a technical advantage in that it can be administered at any time during the patient treatment cycle, whereas for ELISA measurement of IFX trough levels a sample must be collected just before the next dose.

4.4 Cost of Technology and Options

According to information provided by the requestors, the weighted value of the ELISA test is 155.10, and the HPLC-HMSA test is 65.33.

The laboratory of the ELISA test requestor already has the necessary equipment and qualified personnel to perform these assays. There is no commercial quality control program available for the ELISA assays covered by this notice. However, the requestor has implemented a sample exchange program with the GD Specialized Diagnostics laboratory, which will start in the first quarter of 2014. As a result, each lab will assume the cost of 8 additional assays per year.

For the HPLC-HMSA test, the requestor's laboratory already has the necessary equipment and qualified personnel to perform these assays, but the weighted value does not include the cost of an external control program since the requestor has not implemented one yet.

Tests are currently sent outside Quebec, primarily to Prometheus Therapeutics and Diagnostics in the United States. According to information provided by MSSS, the total cost of the 236 assays performed between April 1, 2012, and December 31, 2013, was $261,888.[8] The majority of the cost corresponds to 108 Anser® IFX assays ($206,275); the rest ($55,613) is attributed to 128 ELISA tests. The unit cost of the Anser® IFX assay ranges from $1,400 to $2,500, and the ELISA test varies between $225 and $400.

[8] Information provided by MSSS, Quebec, November 12, 2013.

If the weighted value of the test is considered when performed locally, approximately 1,700 ELISA assays and 4,000 HPLC-HMSA assays could be performed locally for the amount allocated to the 236 tests performed outside Quebec.

5 EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced

Other methods are described in the scientific literature for measuring IFX and anti-IFX: fluid-phase radioimmunoassay, reporter gene assay, and enzyme immunoassay [Steenholdt et al., 2013]. None of these methods are included in the Index.

5.1.2 Diagnostic or Prognostic Value

A meta-analysis of 7 studies of Crohn disease (a total of 11 studies were included) shows a high risk of "loss of response" when anti-IFX antibodies are present in patients with Crohn disease (RR 3.2; 95% CI: 1.9 to 5.5; $P < 0.0001$). The studies were heterogeneous (I^2: 73%). Combining the results of 3 studies revealed a significant difference in minimum serum IFX levels (trough serum concentration observed just before dose administration) between patients with positive antibodies and those with negative anti-IFX antibodies (standardized mean difference: –0.8; 95% CI: –1.2 to –0.4; $P < 0.0001$). Additionally, 8 of the 11 studies used the ELISA test, 2 used radioimmunoassay, and 1 study did not mention technique [Nanda et al., 2013]. A systematic review of 13 studies on the clinical utility of testing levels of antibodies against anti-TNFα drugs in Crohn disease [Chaparro et al., 2012] reported a close relationship between anti-TNFα concentrations and continued therapeutic response. The authors indicated that the role of antibodies in loss of response seems to be limited to their promotion of drug clearance. The risk of injection reactions, but not delayed hypersensitivity reactions, is higher in patients with antibodies against anti-TNFα. The authors concluded that measurement of anti-TNFα and antibody titres seems to be useful in therapeutic monitoring of IFX to optimize treatment and improve clinical management of patients with inflammatory bowel disease. Of the 13 studies included, 10 measured serum antibody levels and their effects on efficacy. However, the methods used in the studies to measure antibodies were not indicated.

The relationship between the presence of anti-IFX antibodies and loss of therapeutic response was assessed in a pilot study of 15 psoriasis patients [Adisen et al., 2010]. An ELISA kit was used to determine the presence of antibodies, and clinical efficacy was assessed with the Psoriasis Area and Severity Index (PASI[9]). Total length of follow-up was not clear. Of the patients with negative antibodies, 10 had received, on average, 5.9 ± 3.2 IFX infusions compared with 9.0 ± 5.2 IFX infusions in the 5 patients with positive antibodies. PASI scores were significantly lower in the "antibody negative" group at the end of follow-up (5.3 ± 2.4 versus 10.0 ± 4.9, $P = 0.02$).

A prospective study determined the relationship between serum TNFα levels and clinical response in 55 rheumatoid arthritis patients treated by IFX [Edrees et al., 2005]. Clinical disease activity was evaluated using the Ritchie score.[10] IFX antibodies were measured by competitive

[9] The Psoriasis Area and Severity Index (PASI) [Fredriksson and Petersson, 1978] is used in dermatology to monitor psoriasis progression and treatment efficacy. The PASI score is based on the number of areas affected (for example: head, arms, trunk, legs), the percentage of skin surface area affected, and the severity of lesions. The final score ranges from 0 (absence of psoriasis) to 72 (severe psoriasis).

[10] The Ritchie Articular Index (RAI) is a tool to assess joint pain in patients with rheumatoid arthritis. It is the sum of the degree of sensitivity in each joint (0 = no pain, 1 = pain on palpation, 2 = pain and wincing, and 3 = wincing and withdrawal) after firm pressure on the periphery of 53 joints (for example, shoulders, elbows, wrists, hips).

ELISA assay immediately before and 9 to 11 days after receiving IFX. Mean post-infusion TNFα serum levels were higher in the group with active disease (Ritchie score > 10) than in the group with inactive disease (Ritchie score ≤ 10) (76.6 ± 93.4 ng/mL versus 26.4 ± 7.9 ng/mL, $P < 0.01$).

A retrospective study of 51 consecutive patients with RA assessed the relationship between anti-IFX antibodies and clinical response [Haraoui et al., 2006]. IFX concentrations were measured using the ELISA method. Total length of follow-up was not clear. Patients were divided into two groups: group 1 (n = 19) included patients who had achieved and maintained clinical response with infliximab at a dose of 3 mg/kg administered every 8 weeks, and group 2 (n = 32) included patients who required higher doses. There were no statistically significant differences in baseline data or clinical characteristics between the groups. Anti-IFX antibodies occurred in 47% of patients in group 2 versus 27% of patients in group 1, with higher mean anti-IFX antibody concentrations in group 2 (18.3 ± 8.9 g/mL versus 7.5 ± 4.8 g/mL, $P = 0.02$).

Serum trough IFX levels and clinical response to IFX treatment were studied prospectively by ELISA in a cohort of 105 patients with RA [Wolbink et al., 2005]. Clinical response was measured by the 28 joint count Disease Activity Score (DAS28) and EULAR response criteria. After 14 weeks, 77 patients had satisfied response criteria. Non-responders had lower serum IFX trough levels than responders – median (interquartile range): 0.5 mg/L (0.2 to 2.2 mg/L) versus 3.6 mg/L (1.4 to 8.2 mg/L), P: 0.01.

No relevant articles on spondyloarthritis were found.

5.1.3 Therapeutic Value

Test results will help determine the effectiveness of IFX treatment and whether treatment modification (change of dose, addition of another anti-TNF, etc.) is required to optimize therapeutic response (morbidity, disability, quality of life, and survival) for several diseases.

A retrospective study was conducted with 155 patients with inflammatory bowel disease and anti-IFX antibodies. IFX concentrations measured during follow-up indicated that, for the 177 tests performed for this group of patients, results affected treatment decisions in 73% of cases, particularly decisions to modify treatment or increase doses [Afif et al., 2010].
An observational study of IFX concentrations to control RA activity in 24 patients [Mulleman et al., 2009] compared treatment decisions made using the DAS28 (number of tender and swollen joints, global assessment of health by the patient, and sedimentation rate or C-reactive protein) with those made using measurements of anti-IFX antibodies (ELISA) and clinical results. Patients were followed for four consecutive visits. The therapeutic decision at the second visit differed from the decision made at the initial assessment for 12 patients (50%). The 6 patients whose dose was reduced returned to the initial dosage, 4 of the 13 patients whose dosage was maintained had the dose increased, and 2 of the 5 patients whose dose was increased returned to the initial dosage.

5.2 Clinical Validity

TERM	PRESENCE	ABSENCE	NOT APPLICABLE
Sensitivity	x		
Specificity	x		
Positive predictive value (PPV)		x	
Negative predictive value (NPV)		x	
Likelihood ratio (LR)		x	
Receiver operating characteristics (ROC) curve	x		
Accuracy		x	

HMSA

Mean IFX antibody levels in patient serum samples were significantly higher than for the drug-naïve, healthy control group (mean ± SD = 9.57 ± 11.43 versus 0.73 ± 0.29 µg/mL, $P < 0.0001$). ROC curve analysis showed that the area under the curve was 0.986 ± 0.007 (95% CI: 0.973 to 0.999; $P < 0.0001$), sensitivity was 95% (95% CI: 88.72% to 98.36%), and the odds ratio (probability of a positive result for someone sick rather than someone healthy) was 47.50 with a cutoff of 1.19 µg/mL [Wang et al., 2012].

A paper presenting the results of a study by Feagan et al. [2012] at the Digestive Disease Week conference (San Diego, California) reported that use of HMSA on 1,487 samples allowed serum trough IFX levels and anti-IFX antibody levels to be correlated with Crohn disease activity level in 483 patients receiving maintenance therapy. The authors reported that 64% of patients presented serum IFX trough levels higher than 3 µg/mL and 24% had anti-IFX antibodies. The authors noted that, in the absence of anti-IFX antibodies, detection of a serum IFX trough threshold level of 3 µg/mL correlated with low levels of C-reactive protein (CRP), a marker for disease activity. Conversely, the presence of anti-IFX antibodies correlated with an increase in C-reactive protein activity, independent of serum IFX levels.

5.3 Analytical (or Technical) Validity

TERM	PRESENCE	ABSENCE	NOT APPLICABLE
Repeatability		x	
Reproducibility		x	
Analytical sensitivity		x	
Analytical specificity		x	
Matrix effect		x	
Concordance	x		
Correlation between test and comparator	x		
Other depending on the type of test	x		

The monograph for the Promonitor® IFX kit [Proteomika, 2013; MyAssays, 2012] provided data on analytical validity compared with a common ELISA test. Data were based on four studies reported in the literature. Based on 277 samples:

- correlation coefficient: 0.961 ($P = 1 \times 10^{-6}$)
- concordance: 97.8%

Sixty-two serum samples and spiked controls were used to evaluate correlation among three ELISA assays for measuring IFX and anti-IFX antibodies [Vande Casteele et al., 2012]. All IFX and IFX antibody assays showed linear quantitative correlation (Pearson *r*), and IFX antibody assays showed concordance between 0.59 and 0.91 (intraclass correlation coefficient) (Table 1).

Table 1: Correlation and concordance among three ELISA assays [Vande Casteele et al., 2012]

	CORRELATION (R)	*P*	CONCORDANCE	95% CI	*P*
IFX Assays					
A versus B	0.91	< 0.0001	0.91	0.86-0.95	< 0.0001
B versus C	0.73	< 0.0001	0.59	0.39-0.73	< 0.0001
A versus C	0.83	< 0.0001	0.73	0.58-0.83	< 0.0001
Anti-IFX Antibody Assays					
A versus B	0.95	< 0.0001	Could not be calculated because the tests gave different result measurements (AU/mL, µg/L)		
B versus C	0.97	< 0.0001			
A versus C	0.99	< 0.0001			

AU = arbitrary unit

One study compared four techniques (fluid phase radioimmunoassay [RIA], ELISA, reporter gene assay [RGA], and enzyme immunoassay [EIA]) for monitoring IFX and anti-IFX antibodies in Crohn disease using samples from 13 patients [Steenholdt et al., 2013]. For measurement of IFX concentrations, coefficients of variation were ≤ 20% for IFX concentrations between 1 and 9 µg/mL. Examined two by two, all tests showed linear correlations (R^2 = 0.97 to 0.99). A statistically significant discrepancy was noted among the three assays when different IFX serum concentrations were tested the same day, on different days, and for different individuals. The maximum difference noted for each pair of assays was 1.55 µg/mL for RIA and RGA, 1.41 µg/mL for ELISA and RIA, and 0.48 µg/mL for ELISA and RGA ($P < 0.05$).

Lower limit of detection: 0.07 µg/mL for RIA, 0.13 µg/mL for RGA, and 0.26 µg/mL for ELISA.
For measurement of anti-IFX antibodies, RGA gave reproducible results (CV ≤ 7%) compared with the other techniques (between 24% and 26%). Of the six pairs of assays, four had linear correlations (R^2 = 0.71 to 0.93), except ELISA versus RGA and EIA. Concordance of anti-IFX antibody titres had a mean difference of –500 (–900 to –100) in RGA and EIA; 1,600 (–1,800 to 5,100) in ELISA and EIA; 2,100 (–1,600 to 5,800) in ELISA and RGA; 2,400 (–5,000 to 200) in ELISA and RIA; 4,000 (500 to 7,600) in RIA and EIA; and 4,500 (600 to 8,400) in RIA and RGA. The authors noted that a contributing factor to these differences was the inability of ELISA to detect IgG4 anti-IFX antibodies.

A single study published by the researchers who developed the assay provided information on the analytical validity of HPLC-HMSA [Wang et al., 2012].

For detection of IFX:
- lower limit of quantification is 0.039 µg/mL in serum;
- intra-assay precision: CV < 6%; accuracy: < 10% error;
- inter-assay precision: CV < 15%; accuracy: < 21% error.

For detection of IFX antibodies:

- lower limit of quantification is 0.012 µg /mL in serum;
- intra-assay precision: CV < 4%; accuracy: < 12% error;
- inter-assay precision: CV < 15%; accuracy: < 21% error.

Additionally, this study correlated anti-IFX antibody values obtained by HPLC-HMSA and bridging ELISA using 100 samples from patients with Crohn disease, and reported a correlation of r = 0.39 (95% CI: 0.2 to 0.55; *P* < 0.0001). After new assays, HPLC-HMSA determined that five samples considered positive with the ELISA test (based on the approach described by Baert et al. [2003, cited in Wang et al., 2012]) were false-positives.

5.4 Recommendations from Other Organizations

The London Position Statement,.issued by the World Congress on Biological Therapy for IBD with the European Crohn's and Colitis Organization in 2010, establishes that high IFX trough concentrations are associated with continued clinical response, and low serum trough concentrations are associated with potential loss of response (level of evidence: 2b on the scale of the Oxford Centre for Evidence-Based Medicine) [D'Haens et al., 2010].

6 OUTCOMES OF INTRODUCING THE TEST

6.1 Impact on Material and Human Resources

Not analyzed.

6.2 Economic Consequences of Introducing Test Into Quebec's Health Care and Social Services System

Introducing the test into the Index would result in a lower cost per test compared with sending assays to laboratories outside Quebec. However, frequency of testing could increase.

6.3 Main Organizational, Ethical and Other (Social, Legal, Political) Issues: Not analyzed.

7 IN BRIEF

7.1 Clinical Relevance

There are several studies for three indications of interest that show the value of measuring IFX and anti-IFX antibody levels for follow-up and clinical management of patients treated with IFX. Most of these studies used ELISA or other methods; few used HPLC-HMSA.

7.2 Clinical Validity

Little data, probably due to the difficulty of defining loss of response for the different indications.

7.3 Analytical Validity

The information available indicates that the accuracy of both tests is good. An expert consulted confirms this information.

7.4 Recommendations From Other Organizations

International organizations recognize the association between IFX concentrations and loss of response in Crohn disease.

8 INESSS NOTICE IN BRIEF

Detection of Infliximab and Anti-Infliximab Antibodies with ELISA or High-Performance Liquid Chromatography

Status of the Diagnostic Technology

☒ Established: ELISA
☒ Innovative: HPLC-HMSA
☐ Experimental (for research purposes only)
☐ Replacement for technology: _____, which becomes obsolete

INESSS Recommendation

☒ Include test in the Index
☐ Do not include test in the Index
☐ Reassess test

Additional Recommendation

☐ Draw connection with listing of drugs, if companion test
☐ Produce an optimal use manual
☐ Identify indicators, when monitoring is required

NOTE

Few data are available for the HPLC-HMSA technique, although it seems superior to ELISA.
Although we have recommended including the test in the Index, the information available does not allow us to give priority to either of the two methods.

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