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Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

Infliximab is an effective treatment for rheumatoid arthritis, ankylosing spondylitis, Crohn's disease (both adult and paediatric), ulcerative colitis, psoriatic arthritis and plaque psoriasis and national and international guidelines have been developed for each indication.

WHAT THIS STUDY ADDS

This study is the first study which compared current international, national and local guidelines from the medical specialties involved in the treatment with infliximab on the following topics: indication, dosage, synergy and monitoring of vital signs.

AIMS

Infliximab, an anti-TNF biologic agent, is currently indicated and reimbursed for rheumatoid arthritis, ankylosing spondylitis, Crohn's disease (both adult and paediatric), ulcerative colitis, psoriatic arthritis and plaque psoriasis. Development of national and international guidelines for rheumatology, gastroenterology and dermatology, was mostly based on clinical studies and expert opinion. The aim of this study was to compare available guidelines and local protocols for rheumatology, dermatology and gastroenterology, regarding dosage of infliximab, synergy of infliximab with concomitant medication and monitoring of vital signs during infliximab administration, for achieving optimal care.

METHODS

Current international, national and local guidelines on the use of infliximab were reviewed and compared, differences and shortcomings were identified, and optimal treatment schedules discussed during a meeting (July 2008) of clinical experts and researchers from three departments of a Dutch university hospital.

RESULTS

Recommended dosages of infliximab are not equal for different indications. Loss of response to infliximab is a common problem encountered within the three medical specialties, but indications for adjustments in treatment schedules are lacking in all of the guidelines. Monitoring of vital signs (blood pressure, pulse, temperature) during infusion with infliximab is common practice and recommended by some guidelines. Routine measurement of vital signs is not of any value in predicting or recognizing acute infusion reactions, in our experience, and this is confirmed by literature on inflammatory bowel disease.

CONCLUSION

Different indications encompass different dosing schedules. National and internal guidelines do not provide advice regarding loss of response. Routine measurement of vital signs during infusion is not valuable in detecting acute infusion reactions and should only be performed in case of an acute infusion reaction. These topics need to be studied in future studies and covered in future guidelines.

Introduction

Rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis and psoriasis are chronic inflammatory diseases. Although the exact causes of these diseases remain unknown, over the past two decades major advances have been made in understanding the inflammatory processes. It is likely that in each of these diseases the innate and adaptive immune system are activated, with subsequent production of pro-inflammatory cytokines, like tumour necrosis factor alpha (TNF-α) [1–3]. Antibodies against TNF-α have been developed for the treatment of several chronic inflammatory diseases, including the monoclonal antibodies infliximab and adalimumab. Infliximab, a chimeric (partly human, partly murine) monoclonal antibody (biological), is the only intravenously administered anti-TNF antibody indicated and reimbursed for all of the following diseases: rheumatoid arthritis, ankylosing spondylitis, Crohn's disease (both adult and paediatric), ulcerative colitis, psoriatic arthritis and plaque psoriasis.

National and international guidelines and consensus statements on the use of infliximab have been developed for each of the three medical specialties involved in treatment with infliximab (i.e. gastroenterology, rheumatology and dermatology) and reflect current use in clinical practice.

In many centres like ours, the care for patients receiving infliximab is combined for patients with auto-inflammatory disorders. This emphasizes the need for a combination of guidelines for the treatment with infliximab for patients with these disorders within the involved medical specialities.

Methods

This paper is the product of an expert panel meeting, held by the authors in July 2008.

The purposes of this meeting were as follows:

- To identify similarities and differences within international, national and local guidelines and additional consensus statements from the medical specialties currently using infliximab as anti-TNF therapy, with regards to:
  - Indications for infliximab
  - Dosage for initial and maintenance therapy
  - Monitoring of vital signs during infusion with infliximab
  - Synergistic effects with concomitant medication use
- To discuss the following topics: optimal dosage of infliximab, monitoring of vital signs and use of concomitant medication.
- To discuss the optimal strategy in patients who have lost response to infliximab.

Members of the panel were selected, based on each member's clinical and/or research experience with use of infliximab, from the departments of rheumatology, gastroenterology and dermatology from our university hospital. Members from each medical field performed a literature search in their own discipline by searching the MEDLINE database until July 2008, using the keyword *'infliximab'*, limiting their search to practical guidelines and consensus statements. Additionally, the National Guideline Clearinghouse, a public resource for evidence-based clinical practice guidelines of the Agency for Healthcare Research and Quality in the United States (http://www.guideline.gov) was searched on guidelines related to infliximab. In addition (local) Dutch guidelines from the medical specialties not accessible by MEDLINE but used in clinical practice were reviewed (for an overview of the reviewed guidelines and consensus statements see Table 1). Regarding these guidelines and consensus statements, we limited ourselves to the previously identified topics, namely indication, dosage, monitoring, synergy and loss of response (i.e. secondary inefficacy). Results were presented and discussed during the panel meeting. Additionally, hiatuses within guidelines and consensus statements were discussed.

Results

Indication

Infliximab was first approved for patients with Crohn's disease in 1998. Approval for other indications followed in the subsequent years (Figure 1). In general, patients not responding to conventional therapy and having a moderate to high level of disease activity are eligible for treatment with a biological like infliximab.

Gastroenterology

Crohn's disease patients with extra-intestinal manifestations and fistulizing disease are especially eligible for treatment with infliximab [4, 5]. Both the international consensus statements of the American Gastroenterological Association (AGA) and the European Crohn's and Colitis Organisation (ECCO) as well as national guidelines agree that treatment with infliximab is appropriate for patients with inflammatory bowel disease experiencing corticosteroid dependency, glucocorticoid and/or immunomodulative treatment refractoriness or active fistula associated with Crohn's disease [4, 6–8].

Rheumatology

In rheumatoid arthritis, the international consensus statement on biologicals for the treatment of rheumatoid arthritis, which is updated nearly every year, does not provide criteria on which patients should be treated with antibodies against TNF-α, like infliximab [9]. National guidelines, however, do provide such criteria. Patients should have failed on at least one (Swedish, French and

Table 1

Summary of reviewed consensus statements and guidelines regarding the use of infliximab

Medical specialty	Study, year published (reference)	Paper	Country
Gastroenterology	Consensus statement		
	ECCO, 2006 [6]	European evidence based consensus on the diagnosis and management of Crohn's disease: current management	Europe
	AGA, 2007 [4]	American Gastroenterological Association Consensus Development Conference on the use of biologics in the treatment of inflammatory bowel disease	International
	Guidelines		
	Hommes *et al.*, 2006 [7]	Guidelines for treatment with infliximab for Crohn's disease	The Netherlands
	Panaccione *et al.*, 2004 [8]	Canadian Association of Gastroenterology clinical practice guidelines: The use of infliximab in Crohn's disease	Canada
Rheumatology	Consensus statement		
	Furst *et al.*, 2008 [9]	Updated consensus statement on biological agents for the treatment of rheumatic diseases	International
	Braun *et al.*, 2006 [18]	First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis	International
	NVR, 2004 [19]	Statement on the application of TNF-blockade in the treatment of ankylosing spondylitis	The Netherlands
	CRA, 2003 [57]	Canadian rheumatology association consensus on the use of anti-tumor necrosis factor-alpha directed therapies in the treatment of spondyloarthritis	Canada
	Guidelines		
	NICE, 2007 [11]	NICE technology appraisal guidance 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis	UK
	NVR, 2003 [12]	Guideline: Application of anti-TNF blockers in the treatment of rheumatoid arthtritis	The Netherlands
	FSR, 2007 [13]	Recommendations of the French Society for Rheumatology regarding TNFalpha antagonist therapy in patients with rheumatoid arthritis	France
	JCR, 2007 [14]	Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis	Japan
	ACR, 2008 [17]	American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis	USA
	NICE, 2008 [23]	NICE technology appraisal guidance 143. Adalimumab, etanercept and infliximab for ankylosing spondylitis	UK
	NICE, 2007 [24]	NICE technology appraisal guidance 104. Etanercept and infliximab for the treatment of adults with psoriatic arthritis	UK
	BSR, 2005 [16]	Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001)	UK
	BSR, 2005 [21]	BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology	UK
	FSR, 2007 [22]	Recommendations of the French Society for Rheumatology regarding TNF alpha antagonist therapy in patients with ankylosing spondylitis or psoriatic arthritis: 2007 update	France
Dermatology	Consensus statement		
	Reich *et al.*, 2008 [25]	Recommendations for the long-term treatment of psoriasis with infliximab: A dermatology expert group consensus	Europe and Canada
	Sterry *et al.*, 2004 [58]	Biological therapies in the systemic management of psoriasis: International Consensus Conference	International
	Guidelines		
	BAD, 2005 [26]	British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005	UK
	NVDV, 2005 [27]	Guideline: Application of biologicals in the treatment of psoriasis	The Netherlands
	AAD, 2008 [36]	Guidelines of care for the management of psoriasis and psoriatic arthritis – Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics.	USA
	NICE, 2008 [59]	Infliximab for the treatment of adults with psoriasis	UK
	AAD, 2008 [60]	Guidelines of care for the management of psoriasis and psoriatic arthritis – Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics	USA

AAD, American Academy of Dermatology; ACR, American College of Rheumatology; AGA, American Gastroenterological Association; BAD, British Association of Dermatologists; BSR, The British Society for Rheumatology; CRA, Canadian Rheumatology Association; ECCO, European Crohn's and Colitis Organisation; FSR, French Society of Rheumatology; JCR, Japan College of Rheumatology; NICE, National Institute for Clinical Excellence; NVDV, Nederlandse Vereniging voor Dermatologie en Verenologie; NVR, Nederlandse Vereniging voor Reumatologie.

Japanese guidelines) or two (British and Dutch guidelines) disease modifying anti-rheumatic drugs (DMARDs), including methotrexate in an adequate dosage and have a disease activity measured by the Disease Activity Score using 28 joint counts (DAS28) [10] of >5.1 (British guidelines) [11–16]. However, according to the Swedish guidelines no specific disease activity is required for starting with biologicals [15]. The consensus statement of The American College of Rheumatology (ACR) recommends starting with anti-TNF therapy like infliximab in cases with 1) high disease activity (DAS28 > 5.1) for 3–6 months, or 2) less than 3 months in combination with features of a poor

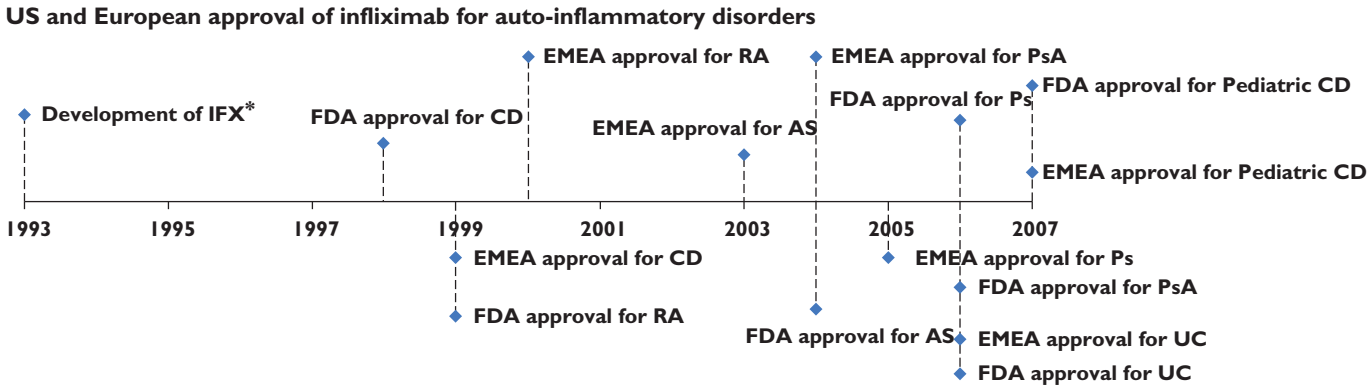

Figure 1

Approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) of infliximab (IFX). AS, ankylosing spondylitis; CD, Crohn's disease; RA, rheumatoid arthritis, UC, ulcerative colitis; Ps, psoriasis; PsA, psoriatic arthritis. * Knight *et al*. [62]

prognosis (e.g. functional limitation, extra articular disease, rheumatoid factor positivity, bony erosions by radiography) or 3) moderate disease activity (DAS28 > 3.2 and <5.1) for >6 months and inadequate response to monotherapy with methotrexate in combination with features of poor prognosis [17].

Ankylosing spondylitis The international consensus statement from Furst *et al*. does not provide criteria for treatment with infliximab in patients with ankylosing spondylitis [9]. However, another international consensus statement from the ASsessment in Ankylosing Spondylitis (ASAS) working group [18], as well as a statement from the Dutch Society for Rheumatology [19] gives clear criteria on the use of infliximab in patients who fulfilled the modified New York criteria for the diagnosis of ankylosing spondylitis [20], including active disease for >4 weeks,(Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4 (0–10) and an expert opinion (the expert should consider clinical features (history and examination), serum acute phase reactant levels and/or imaging results, such as radiographs demonstrating rapid progression or MRI indicating ongoing inflammation). Furthermore, all patients should have had adequate therapeutic trials of at least two NSAIDs, which is defined as:

- Treatment for at least 3 months at maximum recommended or tolerated anti-inflammatory dose unless contraindicated
- Treatment for <3 months where treatment was withdrawn because of intolerance, toxicity or contraindications

The guideline from the French Society for Rheumatology (FSR) is more strict regarding co-medication, stating that patients should have failed at least three NSAIDs used for 3 consecutive months while according to the guidelines from the British Society for Rheumatology (BSR) there should be a failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated/recommended dosage for 4 weeks [21, 22]. Although the guidelines from the BSR recommend treatment with infliximab, the British guidelines from the National Health Service (NHS) state that infliximab is not recommended for the treatment of ankylosing spondylitis [23].

Psoriatic arthritis As for rheumatoid arthritis and ankylosing spondylitis, the international consensus statement from Furst *et al*. does not provide criteria for treatment with infliximab in patients with ankylosing spondylitis [9]. According to the NHS guidelines, patients with psoriatic arthritis are eligible for treatment with infliximab in case of peripheral arthritis with three or more tender joints and three or more swollen joints and the psoriatic arthritis has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination and the patient has been shown to be intolerant of, or have contraindications to, treatment with etanercept or has major difficulties with self administered injections [24]. The FSR guideline is more specific, indicating that the patient must have active and predominantly peripheral disease documented on two occasions at least 4 weeks apart, with both a tender joint count and a swollen joint count of ≥3 on a total of 76/78 joints and have an overall assessment of disease activity by the physician of ≥4 on a 10 point scale. Furthermore there should be persistent evidence of active disease after at least 4 months treatment with MTX in a dosage of ≥15 mg week^{-1}, leflunomide ≥20 mg day^{-1}, or sulfasalazine ≥2 g day^{-1} [22].

Dermatology

Few guidelines and consensus statements on the use of infliximab exist for patients with plaque psoriasis. According to the international consensus statement by Reich *et al*. patients with psoriatic arthritis in association with skin symptoms or moderate to severe psoriasis who have

failed two or more systemic therapies are eligible for treatment with infliximab [25]. Furthermore, patients with a Psoriasis Area and Severity Index (PASI) of ≥20 or patients with an improvement of less than 50% on this scale with previous (non) biological treatment, were eligible for treatment with infliximab [25]. The guideline of the British Association of Dermatologists (BAD) states that patients should have severe disease, defined as a PASI of 10 or more (or a body surface area of 10% or greater where PASI is not applicable) *and a* Dermatology Life Quality Index >10. Secondly, patients should be unresponsive or intolerant to standard therapy [26]. In the Netherlands, patients are eligible for biological therapies if they have a PASI of ≥10, and have failed to respond to phototherapy, methotrexate and ciclosporin in the past, or have a contraindication to, or are intolerant of these treatments [27].

Dosage

The first randomized clinical trial with infliximab (at that time called cA2), in patients with rheumatoid arthritis, randomized patients over a single dose of 1 mg kg^{-1} bodyweight, 10 mg kg^{-1} bodyweight and placebo [28]. In this study, a dosage dependent response was observed. A subsequent study comparing the effect of multiple infusions with infliximab in patients with rheumatoid arthritis compared 1 mg to 3 mg and 10 mg $kg^{-}1$ bodyweight, showing the best results with the latter two [29]. Furthermore it was shown that the median duration of response to the lowest dosage (i.e. 1 mg kg^{-1} bodyweight) lasted 3 weeks, compared with 5 and 8 weeks with dosages of 3 and 10 mg kg^{-1} bodyweight, respectively [30].

Additional studies, performed in patients with Crohn's disease, compared a single dose of 5 mg, 10 mg or 20 mg kg^{-1} bodyweight, administered over a 2 h period. In this trial, patients receiving 5 mg kg^{-1} had the best response to infliximab [31]. An open-label trial in Crohn's disease patients, which was performed earlier, compared doses of 1 mg, 5 mg, 10 mg and 20 mg kg^{-1}. The group receiving 1 mg kg^{-1} had a more transient response than the groups given the higher doses [32].

One of the first case reports of psoriasis patients treated with infliximab reported a significant response with 5 mg kg^{-1} bodyweight and the first randomized trial in patients with psoriasis showed significant responses to 5 mg kg^{-1} and 10 mg kg^{-1} bodyweight [33, 34].

Gastroenterology

With regard to dosing of infliximab in inflammatory bowel disease, as can be seen in Table 2, international and national consensus statement/guidelines recommend a dosage of 5 mg kg^{-1} body weight given in a 0-2-6-weeks induction regimen and followed by maintenance dosing every 8 weeks [4, 7]. The ECCO statement recommends the same dosage, since 5 mg kg^{-1} body weight has been shown effective in large placebo controlled trials [6, 35]. However, this consensus statement gives no information regarding any induction regimen. According to the AGA consensus, primary non response can be determined after two doses [4]. However, the Dutch guidelines recommend assessment of the treatment effect 8 weeks after the third infusion, when infliximab is combined with an immunosuppressant since immunosuppressants such as azathioprine and methotrexate only become effective after about 3 months [7]. When the response is attenuated in patients, dosage can be increased to 10 mg kg^{-1} body weight or the interval between infusions can be shortened up to 4 weeks [6, 7].

Rheumatology

In patients with rheumatoid arthritis, the standard dosage of infliximab administered recommended by most guidelines is 3 mg kg^{-1} bodyweight in an induction regimen at 0, 2 and 6, and thereafter every 8 weeks [11, 13, 14]. Some of the national and international guidelines do not explicitly state that infliximab should be administered at 3 mg kg^{-1} bodyweight, but rather assume that clinicians will administer this 'standard dosage' [9, 12, 17]. As for patients with inflammatory bowel disease, if guidelines refer to attenuation of response, the dosage should be increased or the dosing interval shortened, together with the addition or substitution of another DMARD [9]. The Japanese guideline, however, does not allow any increment of dosage or shortening of interval, and some guidelines do not give recommendations regarding this topic [12, 14, 17]. The National Institute for Clinical Excellence (NICE) guideline is most explicit in its recommendation, recommending increasing the dose of infliximab stepwise by approximately 1.5 mg kg^{-1}, up to a maximum of 7.5 mg kg^{-1} every 8 weeks, or alternatively administering of 3 mg kg^{-1} as often as every 4 weeks [11]. Recommended dosages from the reviewed guidelines and consensus statements regarding the specific diseases as well as the recommended dosage from the manufacturer are given in Table 2.

Dermatology

The guidelines on the treatment of psoriasis with biologicals from the American Academy of Dermatology (AAD), BAD and the international consensus panel of dermatology experts advises dosing infliximab in a 5 mg kg^{-1} infusion schedule at 0, 2 and 6 weeks, followed by maintenance treatment every 6–8 weeks (Table 2) [25, 26, 36]. The British guidelines however, state that no studies have been performed to establish the optimal dose or frequency of repeated infusions required in order to achieve disease control [26]. The dermatology guidelines give no clear recommendation regarding how to manage attenuated response to infliximab (Table 2).

Table 2

Statements from guidelines and consensus statements for different auto-inflammatory disorders on issues related to the use of infliximab: dosage regimen, induction therapy, loss of response, loss of response and the use of concomitant medication

Indication	Study, year (reference)	Dosage (mg kg^{-1})	Induction therapy (weeks)	Maintenance intervals (in weeks)	Determination of (non) response*	Advice regarding loss of response in patients who initially responded to IFX	Recommended co-medication
CD	Centocor, 2009 [61]	5	0,2,6	8	Active Crohn's disease: after two doses Fistulizing disease: after three doses	Some patients may regain response with dose escalation.	NA
	ECCO, 2006 [6]	5	NA	8	NA	Most try increasing the dose to 10 mg kg^{-1}	AZA, MP or MTX
	AGA, 2007 [4]	5	0,2,6	8	After two doses	Patients who have attenuated response may be given - higher dose infusions up to 10 mg kg^{-1} at 8-week intervals, or - 5 mg kg^{-1} at shortened intervals as frequently as every 4 weeks.	Initiated in advance of biologic therapy
	Hommes *et al.*, 2006 [7]	5	0,2,6	8	4 weeks after the second infusion	Increase to 10 mg kg^{-1} on strict verified indication.	Use of an immunosuppressant.
	Panaccione *et al.*, 2004 [8]	5	0,2,6	8	After three doses	Dosage increasement to 10 mg kg^{-1} or shortening of infusion intervals	Concomitant immunosuppressive therapy (eg, 6-MP, AZA or MTX)
UC	Centocor, 2009 [61] AGA, 2007 [4]***	5	0,2,6	8	After three doses	NA	NA
RA	Centocor, 2009 [61]	3	0,2,6	8	12 weeks	Options: - Increase the dose step-wise by approximately 1.5 mg kg^{-1}, up to a maximum of 7.5 mg kg^{-1} every 8 weeks *or* - Administration of 3 mg kg^{-1} as often as every 4 weeks may be considered.	MTX
	Furst *et al.*, 2008 [9]	NA	NA	NA	Within 12–24 weeks	Increasing the dose or reducing the dosing intervals may provide additional benefit in RA, as may the addition or substitution of other DMARDs.	MTX
	NICE, 2007 [11]	3	0,2,6	8	6 months	Options: - Increase the dose step-wise by approximately 1.5 mg kg^{-1}, up to a maximum of 7.5 mg kg^{-1} every 8 weeks *or* - Administration of 3 mg kg^{-1} as often as every 4 weeks may be considered.	MTX
	NVR, 2003 [12]	NA	NA	NA	12 weeks	Increasing dose or reducing the infusion intervals	NA
	FSR, 2007 [13]	3	0,2,6	8	12 weeks	Changes can be made in the dosing interval (every 6 to 8 weeks) or dosage (3 to 5 mg kg^{-1}), or the patient can be switched to another TNFα antagonist	MTX or another DMARD
	JCR, 2007 [14]	3	0,2,6	8	NA	Increment of dosage or shortening of interval is not allowed	MTX at a dose of 6–8mg week^{-1}
	ACR, 2008 [17]	NA	NA	NA	NA	NA	MTX
	BSR, 2005 [16]	NA	NA	NA	3 months	NA	MTX

AS	Centocor, 2009 [61]	5	0,2,6	6 to 8	After two doses	NA	NA
	Furst *et al*., 2008 [9]	5	0,2,6	6 to 8	6–12 weeks	NA	None
	NICE, 2008 [23]	**Infliximab is not recommended for the treatment of ankylosing spondylitis**					
	FSR, 2007 [22]	NA	NA	NA	6–12 weeks	Changes in dosage or dosing interval or the the patient can be switched to another TNFα antagonist	None
	Braun *et al*., 2006 [18]	5	NA	6 to 8	6–12 weeks	NA	None
	BSR, 2005 [21]	5	0,2,6	6 to 8	12 weeks and every 3 months thereafter	NA	NA
	NVR, 2005 [19]	5	0,2,6	6	6–12 weeks and every 6 months thereafter	NA	None
	CRA, 2002 [57]	5	0,2,6	8	NA	NA	None
PsA	Centocor, 2009 [61]	5	0,2,6	8	NA	NA	MTX
	AAD, 2008 [60]	5	0,2,6	6 to 8	NA	Dose and interval of infusion may be adjusted as needed.	NA
	FSR, 2007 [22]	NA	NA	NA	6–12 weeks	Changes in dosage or dosing interval or the the patient can be switched to another TNFα antagonist	None
	NICE, 2007 [24]	5	0,2,6	8	12 weeks	NA	MTX****
	Furst *et al*., 2008 [9]	NA	NA	NA	NA	NA	NA
Ps	Centocor, 2009 [61]	5	0,2,6	8	14 weeks (four doses)	NA	None
	Reich *et al*., 2008 [25]	5	0,2,6	8	12 weeks (or three doses)	Decreasing the interval between infusions (e.g. from every 8 weeks to every 6 weeks), increasing the dose of drug administered and/or introducing a supplementary therapy such as a topical treatment or MTX.	None
	BAD, 2005 [26]	5	0,2,6	8	NA	NA	*****
	NVDV, 2005 [27]	3–10 mg kg^{-1}**	0,2,6	8	8 weeks	NA	None
	AAD, 2008 [36]	5	0,2,6	6 to 8	NA	Dose and interval of infusion may be adjusted as needed.	NA
	Sterry *et al*. 2004 [58]	5 or 10	0,2,6	NA	NA	NA	NA
	NICE, 2008 [59]	5	0,2,6	8	10 weeks	NA	NA

*Period after which treatment with IFX should be stopped in case of non-response. **A definitive recommended dose has not been determined yet. ***See section on Crohn's disease. No distinction is made in the AGA consensus statement between Crohn's disease and ulcerative colitis. ****Following the Summary of Product Characteristics. *****Concomitant systemic therapies may be indicated for some patients with very severe unstable psoriasis, although doses of these should be minimized. AZA, azathioprine; MP, mercaptopurine; MTX, methotrexate; NA, no advice given.

Synergy

Repeated administration of infliximab has been associated with immunogenicity, i.e. the formation of antibodies to infliximab (ATI also known as HACA; human anti-chimeric antibodies). The concomitant use of immunosuppressants may increase the efficacy of infliximab, partly because it prevents the development of immunogenicity, and partially by other mechanisms currently unknown [37–39].

Gastroenterology

The international ECCO guideline has been very clear and advocates that every patient receiving infliximab should receive an immunomodulator (i.e. azathioprine, methotrexate or 6-mercaptopurine) in order to prevent development of antibodies against infliximab that in turn may reduce efficacy and increase side effects [6]. The consensus statement of the AGA strongly recommends co-administration with immunosuppressive therapy as well [4]. The Canadian guidelines are most clear by recommending that all patients, even if they failed to respond to immunomodulators in the past, should receive concomitant immunosuppressants [8]. The Dutch national guideline recommends initiation of immunosuppressants prior to infliximab in order to reduce the formation of antibodies [7].

Rheumatology

Nearly all efficacy studies with infliximab in rheumatoid arthritis patients have been performed in patients receiving concomitant methotrexate [29]. Therefore, all international, national and local guidelines recommend concomitant treatment with methotrexate in case of starting treatment with any anti-TNFα agent, including infliximab [13, 17].

Dermatology

The AAD does not recommend concomitant prescription of low-dose methotrexate, although some dermatologists do so to decrease the formation of antibodies [36]. The international consensus statement on the treatment of psoriasis with infliximab does not provide guidelines on the use of concomitant medication and the British guideline states that concomitant systemic therapies may be indicated for some patients with very severe or unstable psoriasis, although doses should be minimized [25, 26].

Monitoring of vital signs

As a foreign protein-derived agent administered intravenously over a 2 h infusion period, infliximab can cause infusion reactions. Formation of antibodies to infliximab may increase the risk of infusion reactions [37, 39]. These infusion reactions can be categorized as acute or delayed. An acute infusion reaction is defined as any adverse event occurring during infusion or within a period of 24 h after infusion [37, 40]. Severity can vary from mild to severe life threatening, and symptoms may include nausea, flushing, dizziness, dyspnoea, chest pain and hypotension or hypertension. Delayed infusion reactions are defined as reactions occurring from 24 h to 14 days after treatment with infliximab and symptoms may include arthralgia, rash, myalgia and fatigue [37, 40].

In randomized controlled trials with infliximab, vital signs (blood pressure, body temperature and pulse) were monitored vigorously. Monitoring body temperature at baseline is performed to rule out fever possibly based on infection and monitoring during infusion is performed while concerns exist about developing fever during an acute infusion reaction. The monitoring of blood pressure and pulse is based on the concern that during infusion with infliximab an anaphylactic shock could develop with typical hypotension.

Gastroenterology

Study protocols with infliximab in inflammatory bowel disease patients and some experts state that 30 min prior to, every 30 min during infusion and up till 2 h after infusion, vital signs (blood pressure, body temperature and pulse) should be monitored [41]. Randomized controlled trials in patients with inflammatory bowel disease reported incidences of acute infusion reactions ranging from 9–17% [35, 42]. In clinical practice the overall incidence of acute infusion reactions with infliximab is approximately 4–10% [40, 43]. None of the international or national guidelines state that during infusion, vital signs should be monitored. However, in general it is common practice to monitor vital signs during infusion with infliximab.

Rheumatology and dermatology

As in gastroenterology, current practice in rheumatology and dermatology is to monitor vital signs of patients during infusion with infliximab. However, none of the guidelines give specific recommendations regarding monitoring of vital signs.

Interpretation

With the exception of patients treated for rheumatoid arthritis who are treated with a dosage of 3 mg kg^{-1} bodyweight, all patients who are treated with infliximab receive a dosage of 5 mg kg^{-1} bodyweight (Table 2). To our knowledge, however, randomized controlled trials comparing response rates between 3 mg kg^{-1} or 5 mg kg^{-1} in patients with inflammatory bowel disease, rheumatoid arthritis or psoriasis have not been performed. Klotz *et al.* reviewed the current knowledge on clinical pharmacokinetics of

infliximab and stated that little detailed information was available yet and was solely based on measurements of serum concentrations by ELISA using monoclonal antibodies [44]. Indeed, several studies in patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriasis have shown that there is an inter-individual variability of infliximab pharmacokinetics associated with an increase in clinical response with infliximab trough serum concentrations [45–49]. In these studies, however, some patients showed good clinical response to infliximab with undetectable serum concentrations of infliximab, indicating that the correlation between serum concentrations and clinical response is still imprecise. On the other hand, a small observational open label study in patients with rheumatoid arthritis routinely treated with infliximab, showed that the measurement of trough infliximab concentration modified the therapeutic decision for half of their patients and led to improved control of disease activity for patients for whom infliximab dosage was increased [50]. Furthermore with regards to the pharmacokinetics of infliximab, the presence of ATI or HACA, which is associated with an increased risk of infusion reactions and a reduced duration of response, alter the pharmacokinetics of infliximab by an approximately 2.7 fold increase in systemic clearance [51]. Taken together, these findings indicate that further investigations regarding the pharmacokinetics and pharmacodynamics of infliximab are warranted in order to individualize the dosage, based on at least the trough serum concentration and the existence of ATI, thereby optimizing clinical response and cost effectiveness.

Regarding attenuation of response, the guidelines of each specialty recommend dosage increase or interval shortening or changing to another biological therapy. However, there is no clear recommendation which option should be chosen in which subset of patients. Pharmacokinetic modelling of infliximab in patients with rheumatoid arthritis showed that interval reduction might be more effective in raising serum infliximab concentrations than dosage increase [46]. Flendrie *et al*. observed in an open-label study a more pronounced efficacy in patients with rheumatoid arthritis receiving interval reduction, compared with patients receiving a dosage increase [52]. These observations need to be studied in large randomized trials.

With the exception of ankylosing spondylitis, the need for concomitant administration of immunosuppressants during treatment with infliximab has been stressed by most of the guidelines throughout the different specialties, since it appears to prevent the development of antibodies against infliximab [37–39]. However, benefits and risks of combined strategies should be balanced carefully as the evidence for increased risks of combined therapies is growing. This is most established for serious infections, which is observed in patients with inflammatory bowel disease [53, 54].

Table 3

Conclusions and recommendations

Topics	Conclusions and recommendations
Dosage of infliximab	Based on several controlled clinical studies, certain standard dosage regimens for infliximab have been defined which probably need some re-evaluation in terms of improving benefit : risk ratios [44]. Future studies are needed to study the pharmacokinetic–pharmacodynamic relationship of infliximab as a necessary step before therapeutic drug monitoring can be recommended in guidelines.
Monitoring vital signs	Routine scheduled measurement of vital signs during infusion is not valuable in detecting acute infusion reactions and should only be performed in the case of an acute infusion reaction We recommend to administer infliximab at an infusion unit under supervision of trained personnel. This approach enables direct interventions in case a patient reports symptoms. Baseline assessment of patients, including vital signs, should still be performed as normal clinical practice to rule out possible infections or other contraindications for infusion with infliximab.
Use of concomitant medication	Efforts should be made to establish a reasonable time interval in which concomitant medication should be decreased.
Loss of response to infliximab	Although some evidence exists that interval reduction might be more effective in raising serum infliximab concentrations than dosage increase, large randomized trials are needed to observe whether or not interval reduction is superior to dosage increase and in which subset of patients, in order to be able to give guidance regarding loss of response in clinical guidelines.

Monitoring of vital signs during infusion with infliximab is based on strict regulations during clinical trials and still advocated in some treatment algorithms and guidelines [8, 41]. We recently showed that scheduled monitoring of vital signs during infusion did neither indicate nor predict development of acute infusion reactions [55]. When baseline vital signs from patients with and without acute infusion reactions were compared, no significant differences were observed. Furthermore, during an acute infusion reaction, vital signs did not show a significant change compared with baseline [55].

In conclusion, by reviewing current guidelines and consensus statements within the medical specialties of rheumatology, gastroenterology and dermatology on the use of infliximab for auto-inflammatory disorders, several topics (i.e. dosage of infliximab, monitoring of vital signs, use of concomitant medication and loss of response) were discussed and shortcomings in guidelines and consensus statements regarding these topics were identified. Based on this discussion, several recommendations have been made, as can be seen in Table 3. Finally, as stressed by a

recent quality appraisal of clinical practice guidelines and consensus statements on the use of biological agents in rheumatoid arthritis, guidelines should be explicit in their guidance [56], which has implications for the development of future guidelines.

Conflicts of interest

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