

Review and expert opinion on prevention and treatment of infliximab-related infusion reactions

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Summary

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Infliximab (Remicade®; Schering-Plough, Kenilworth, NJ, U.S.A.) is a chimeric monoclonal antibody that acts as a tumour necrosis factor- α inhibitor. Infliximab is registered for the treatment of rheumatoid arthritis, psoriatic arthritis, Crohn disease, ulcerative colitis, ankylosing spondylitis and plaque-type psoriasis. Like other foreign protein-derived agents, infliximab may lead to infusion reactions during and after infusion. Infusion reactions occur in 3–22% of patients with psoriasis treated with infliximab. Most of these reactions are mild or moderate and only few are severe. Nevertheless, they may lead to discontinuation of treatment. As infliximab for psoriasis is prescribed as a last resort and is in most cases very effective, discontinuation of treatment is undesirable. With proper care and prevention of the infusion reactions the need to discontinue treatment with infliximab can be diminished. The objective of this article is to present a guideline for the management of infliximab-related infusion reactions, based on the best available evidence. This guideline can be used in patients with psoriasis as well as in dermatology patients receiving infliximab for off-label indications such as hidradenitis suppurativa or pyoderma gangrenosum.

Infliximab (Remicade®; Schering-Plough, Kenilworth, NJ, U.S.A.) is a chimeric monoclonal antibody (75% human, 25% mouse) that acts as a tumour necrosis factor- α inhibitor. Infliximab is registered for treatment of rheumatoid arthritis (RA), psoriatic arthritis, Crohn disease, ulcerative colitis, ankylosing spondylitis and plaque-type psoriasis. In dermatology it is also used for off-label indications such as hidradenitis suppurativa and pyoderma gangrenosum among others.¹ Infliximab has proven to be very effective in the treatment of moderate to severe chronic plaque-type psoriasis. In several randomized controlled trials (RCTs) around 80% of patients showed an improvement of at least 75% in the Psoriasis Area and Severity Index (PASI 75) after 10 weeks of treatment, and more than half of the patients even showed an improvement of more than 90% (PASI 90).^{2–4}

During and after the intravenous administration of infliximab infusion reactions can occur, comparable with what happens when using other foreign protein-derived treatments. Infusion reactions during the infusion or in the first 24 h afterwards are defined as acute reactions.^{5,6} The majority occurs during or in the first 2 h after the infusion. Symptoms include 'flushing', chest tightness, dizziness, shortness of breath, headache, hypo/hypertension, nausea, sweating, rise in temperature and (other) symptoms of anaphylaxis, like urticaria and bronchospasms.^{3,5,7} Delayed reactions are reactions that occur between 24 h and 14 days after an infusion,

the majority occurring after 5–7 days.⁵ In most cases symptoms include arthralgia, myalgia, influenza-like symptoms, headache, tiredness and 'rash' or urticaria.^{4,5,8}

Infusion reactions appear in 3–22% of patients with psoriasis who are treated with infliximab;⁷ in placebo arms this is approximately 0–2%.^{3,4} The reactions can be subdivided into mild, moderate or severe reactions. Most reactions are mild or moderate and only few are severe.³ The severity of infusion reactions is assigned by the physician based on the patient's signs and symptoms; however, they do not always fit neatly into the definition of mild, moderate or severe reactions.⁶ Mild reactions can be defined as reactions that are self-limiting and resolve spontaneously after temporary cessation of the infusion or reduction of the infusion speed. Moderate reactions are those that require closer attention and an extended observation period and often discontinuation of the infusion. Serious reactions involve respiratory symptoms or a symptomatic blood pressure drop and need for close monitoring, often for 24 h and occasionally requiring hospital admission.⁹ A severe infusion reaction can be anaphylactic or anaphylactoid and should be treated as such (Fig. 1). In these cases infliximab should be stopped immediately.⁵

In an RCT with infliximab 1% of patients with psoriasis developed a severe infusion reaction; similar percentages are seen in patients who are treated with infliximab for other indications.⁴ Also the symptoms^{3,4} and mechanisms of

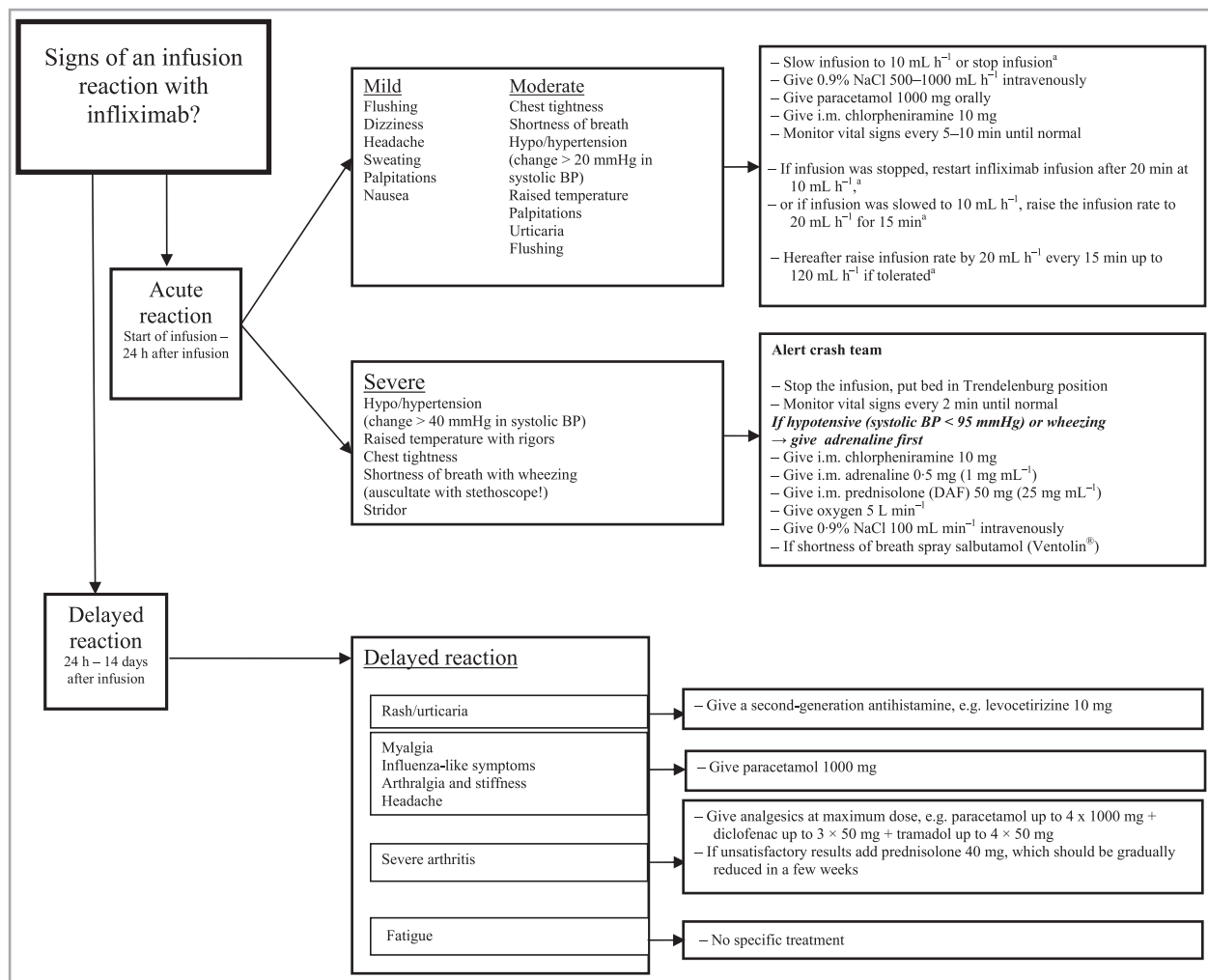


Fig 1. Flowchart for the management of infliximab infusion reactions. ^aThe infusion rates advised are based on the dose of infliximab (x mg) being dissolved in 250 mL of 0.9% saline. BP, blood pressure; i.m., intramuscular.

infusion reactions are thought to be comparable for all patients treated with infliximab, independent of indication for use. The exact mechanisms of infusion reaction development, however, are not yet clear, although several factors and possible mechanisms have been suggested. These include anaphylactic/anaphylactoid reactions, serum sickness-like reactions and development of IgG antibodies against infliximab. These factors and mechanisms will be described in more detail.

Factors and mechanisms

Anaphylactic and anaphylactoid reactions

An anaphylactic reaction is defined as an acute systemic reaction caused by the massive release of histamine and other cytokines from mast cells, mediated by IgE.¹⁰ Bronchospasms and urticaria are typical symptoms of an IgE-mediated anaphylactic reaction, or type I hypersensitivity reaction.⁶ An acute infusion reaction to infliximab is often accompanied by symptoms suggestive of an anaphylactic reaction, and several

anaphylactic reactions to infliximab have been described in the literature.^{11–16} However, IgE antibodies were only demonstrated in one case,¹⁷ and in the other cases proof of IgE mediation was lacking.

Some authors argue that there are several observations that indicate that most anaphylactic-like reactions to infliximab are not true type I hypersensitivity reactions.^{5,6,18,19} First of all, symptoms of an acute infusion reaction often disappear after diminishing the infusion rate, which does not fit with an IgE-mediated reaction. Secondly, in a cohort of 20 patients, normal serum tryptase levels were found after an acute anaphylactic-like reaction, which is inconsistent with an IgE-mediated reaction.⁶ Thirdly, for an anaphylactic reaction previous antigen exposure is needed; acute anaphylactic-like infusion reactions, however, have also been described during first infusions.^{6,13,19} In the cases mentioned, reactions are more likely to be anaphylactoid than anaphylactic. Anaphylactoid reactions are acute systemic reactions that cannot be distinguished clinically from anaphylactic reactions, but are not IgE mediated. It is assumed that these reactions are a result

of direct degranulation and activation of mast cells caused by the involved drug itself. Similarly to anaphylactic reactions, anaphylactoid reactions are serious and potentially life threatening.¹⁰

Serum sickness-like reactions

Serum sickness is a type III hypersensitivity reaction. The disease is the result of tissue deposition of circulating antigen–antibody complexes. Laboratory evaluation usually demonstrates evidence of inflammation (elevated C-reactive protein levels), presence of immune complexes (elevated percentages on C1q binding assay), and activation of the classical pathway of complement (reduced C3 and C4 levels).²⁰

Typical symptoms of serum sickness are rash, fever, and polyarthralgias or polyarthritis. These symptoms begin 1–2 weeks after first exposure to the agent responsible and resolve within a few weeks after discontinuation. A delayed infusion reaction to infliximab clinically imitates serum sickness.^{5,21} However, in delayed infusion reactions the characteristic laboratory findings have not been demonstrated, and therefore these reactions are mostly called serum sickness-like reactions. It has been suggested by Cheifetz *et al.*⁶ that these are mild type III hypersensitivity reactions in which the limitation in diagnosis might be the laboratory processing.

Antibodies to infliximab

Treatment with infliximab can result in the development of human antichimeric antibodies, mostly called antibodies to infliximab (ATI).²² In most patients these antibodies develop soon after initiation of treatment.²³ It has clearly been shown that the presence of ATI increases the incidence of infusion reactions.^{4,5,23–25} In a retrospective cohort study from Baert *et al.*²³ a strong relation between the concentration of ATI and the incidence of infusion reactions was shown. The median concentration of ATI was $20.1 \mu\text{g mL}^{-1}$ when a first infusion reaction occurred, as compared with $3.2 \mu\text{g mL}^{-1}$ among patients without an infusion reaction ($P < 0.001$). Concentrations of $8 \mu\text{g mL}^{-1}$ or higher predicted a high risk of infusion reactions ($P < 0.001$).²³ In an observational study Farrell *et al.* found a 40% incidence of infusion reactions in ATI-positive patients compared with 4.7% in ATI-negative patients ($P = 0.0001$), including serious infusion reactions 28% vs. 0%, respectively ($P = 0.0001$).²⁴

ATI are especially associated with mild to moderate infusion reactions, not with the severe reactions.²⁶ ATI have been demonstrated in 7–61% of patients with psoriasis, Crohn disease and RA.^{11–16} These widely diverging incidences of ATI development can be attributed to the varying presence of risk factors for their development and the many differences between the study populations concerning, for example, treatment schedule, dosing and comedication. The separate risk factors will be discussed further on in this article.

The objective of this article is to present a guideline of how to diminish the chance of infusion reactions and how

to manage these reactions if they do occur. Although available for several indications, there is no specific guideline for the treatment of infliximab-related infusion reactions in dermatology patients. Such a guideline is important as adequate prevention and management of infusion reactions reduce the necessity for treatment discontinuation. This is even more relevant when considering the fact that infliximab is usually one of the last treatment options. We based our guideline on the best available evidence from a review of the literature concerning infusion reactions in patients with psoriasis and other diseases such as Crohn disease and RA, as well as our expert opinion.

Search strategy

Searches in PubMed were conducted using the term 'infliximab', separately and combined with 'infusion reaction', 'anaphylaxis', 'serum sickness', 'antibodies to infliximab', 'methotrexate', 'corticosteroids', 'maintenance', 'intermittent', 'premedication', 'prednisone' and 'immunogenicity'. Articles were selected based upon the relevance of the title and abstract. Relevant articles were focused on safety, especially infusion reactions and large RCTs. The levels of evidence were determined on the 'Oxford Centre for Evidence-based Medicine Levels of Evidence' (May 2001).

Prevention of infusion reactions

Premedication

Premedication is often routinely given before infusions, consisting of paracetamol, antihistamines and/or corticosteroids, to prevent the occurrence of infusion reactions. However, solid evidence that prophylactic medication can prevent infusion reactions is lacking. No RCTs have been conducted comparing patients treated with and without antihistamines and/or paracetamol as prophylactic premedication before infusion. One double-blind RCT has been performed comparing the prophylactic administration of betamethasone (0.15 mg kg^{-1}) before infusion with placebo. There was no significant difference between the groups and the incidence of infusion reactions was even higher in the betamethasone group.²⁷ In another double-blind RCT patients were premedicated with intravenous hydrocortisone or they received a placebo infusion before the administration of infliximab. The hydrocortisone group did experience a lower percentage of infusion reactions (24% vs. 15%) but these results were also not significant.²⁴ In a prospective open-label trial, some of the patients were premedicated with an antihistamine at week 6 and 14 and the rest of the patients was not. The incidences of infusion reactions in the two groups varied only by 0.4%²⁸ (Table 1). Without evidence of a protective effect of premedication it is doubtful whether patients should routinely be given prophylactic premedication. Although low-risk therapeutic agents, the risk of potential side-effects cannot be justified if there is no proven contributive value. The possible

Table 1 Premedication and the incidence of infusion reactions

Reference	Level	Cohort	Study type	Premedication	% IR, group A	% IR, group B	P-value
Sany <i>et al.</i> ²⁷	1B	n = 355, RA	DB PL RCT	A. Oral betamethasone 0.15 mg kg ⁻¹ 30 min pre-infusion B. No premedication	16.8	10.2	0.28 (NS)
Farrell <i>et al.</i> ²⁴	1B	n = 80, CD	DB PL RCT	A. Hydrocortisone 200 mg i.v. immediately prior to infusion B. No premedication	15	24	0.06 (NS)
Wasserman <i>et al.</i> ²⁸	2B	n = 113, RA	Prosp cohort	A. Diphenhydramine 25 mg (95%) or 50 mg (25%) i.v. 30 min pre-infusion B. No premedication	14.7	14.3	

CD, Crohn disease; DB, double blind; IR, infusion reaction; i.v., intravenous; NS, not significant; PL, placebo controlled; Prosp, prospective; RA, rheumatoid arthritis; RCT, randomized controlled trial.

prophylactic effect of premedication after a long infliximab-free interval has not yet been studied.

Infusion schedule

The schedule of infliximab administration has also been pointed out to have an influence on ATI development and infusion reactions.^{5,6,21} It is generally assumed that loading the infliximab therapy with three infusions at weeks 0, 2 and 6 is less immunogenic than only one starting dose. This indeed seems to be the case; however, convincing evidence cannot be found. In a retrospective cohort study with 28 children with Crohn disease Candon *et al.*¹⁷ showed that with a loading schedule (weeks 0, 2 and 6) ATI were formed in 16% of these children while 78% of the children who had only one initial infusion had these antibodies. In an RCT with 53 patients with Crohn disease ATI formation was lower if a second infusion had been given within 8 weeks of the first infusion.²⁴ The same conclusion was reached in a retrospective cohort study regarding a second infusion within 20 weeks following the first infusion.²¹

Also, maintenance treatment (an infusion every 8 weeks) is generally advised instead of on-demand treatment to prevent ATI formation and infusion reactions. The only comparative study on this subject that we found was an RCT with 835 patients with psoriasis. The patients received maintenance treatment every 8 weeks or on-demand treatment after a loading scheme (weeks 0, 2 and 6) at two different dosages (3 or 5 mg kg⁻¹). The percentages of ATI formation after maintenance or episodic treatment were conflicting for the two different dosages. Infusion reactions for both dosages were seen more in the on-demand groups compared with the maintenance groups (no significance given).²⁶ Several dosing schedules were compared in a double-blind RCT with 573 patients with Crohn disease who received a loading dose followed by maintenance treatment or one initial infusion followed by on-demand treatment after week 14. The formation of antibodies was significantly lower in the loading plus maintenance group; however, the

percentages of infusion reactions were the same. These results may be influenced by the fact that 49% of the patients of the second group did not receive a second infusion²⁵ (Table 2).

Overall, the formation of ATI indeed seems to be higher with one initial infusion instead of loading and higher with on-demand instead of maintenance treatment. Also there is a trend indicating that more infusion reactions develop without loading and maintenance treatment, but good comparative clinical studies are definitely necessary. The dosage of infliximab (3 or 5 mg kg⁻¹) does not seem to influence the formation of ATI or the development of infusion reactions^{3,25,28} (Table 2).

Immunosuppressants

Comedication with immunosuppressants is thought to reduce the immunogenicity of infliximab. In patients with psoriasis no studies have been performed combining an immunosuppressant with infliximab. However, several studies with patients with Crohn disease and RA treated with infliximab and methotrexate, systemic corticosteroids and/or 6-mercaptopurine/azathioprine have been published. Of these comedications, only methotrexate is used also for psoriasis on a routine basis. ATI formation was significantly lower in patients comedicated with methotrexate in the prospective cohort study of Vermeire *et al.*²⁹ The same trend was shown by Bendtzen *et al.*,³⁰ but these results were not significant. Kapetanovic *et al.*⁹ retrospectively studied 213 patients with RA and concluded that treatment with infliximab without methotrexate is an independent risk factor for development of infusion reactions (odds ratio 3.1, $P = 0.002$). This conclusion was confirmed by Vermeire *et al.*²⁹ who showed that 16% of patients with methotrexate developed infusion reactions compared with 40% without methotrexate (significant). Crandall and Mackner³¹ added a time factor to the preventive effect of immunosuppressants: after more than 4 months of concomitant immunosuppressive therapy the risk of infusion reactions was lower than before these 4 months.

Table 2 Development of antibodies to infliximab (ATI) and infusion reactions with different dosages and infusion schedules

Reference	Level	Cohort	Study	Dose (mg kg ⁻¹)	Comparative groups	% ATI, group A	% ATI, group B	P-value	% IR, group A	% IR, group B	P-value
Candon <i>et al.</i> ¹⁷	2B	n = 28, pCD	Retr cohort	5	A. Loading week 0, 2, 6 B. One dose	15.7	77.7	0.0028 (S)			
Kugathasan <i>et al.</i> ²¹	2B	n = 86, (p)CD	Retr cohort	5	A. One dose, second dose < 20 weeks B. One dose, second dose > 20 weeks				1.4	53.8	< 0.001 (S)
Menter <i>et al.</i> ²⁶	1B	n = 835, Pso	DB RCT	3	A. Loading week 0, 2, 6 + maintenance every 8 weeks B. Loading week 0, 2, 6 + episodic infusions	51.5	46.2		20	28.9	
				5	A. Loading week 0, 2, 6 + maintenance every 8 weeks B. Loading week 0, 2, 6 + episodic infusions	35.8	41.5		18.9	21.4	
Hanauer <i>et al.</i> ²⁵	1B	n = 573, CD	DB RCT	5/10	A. Loading week 0, 2, 6 + maintenance every 8 weeks B. One dose + episodic infusions > week 14	10 (5 mg); 7 (10 mg)	30 ^a (5 mg)	< 0.0001 (S)	7 (5 mg); 5 (10 mg)	7 ^a (5 mg)	NS
Gottlieb <i>et al.</i> ³	1B	n = 249, Pso	DB RCT	3/5	A. Loading week 0, 2, 6, 3 mg kg ⁻¹ + one infusion on demand > week 26 B. Loading week 0, 2, 6, 5 mg kg ⁻¹ + one infusion on demand > week 26	27.6	19.5		18.4	22.2	
Wasserman <i>et al.</i> ²⁸	2B	n = 113, RA	Retr cohort	3/5	A. Loading week 0, 2, 6, 3 mg kg ⁻¹ B. Loading week 0, 2, 6, 5 mg kg ⁻¹ A. Maintenance 3 mg kg ⁻¹ > week 14 B. Maintenance 5 mg kg ⁻¹ > week 14				8	10.3	> 0.05 (NS)
Maini <i>et al.</i> ⁴⁵	1B	n = 101, RA	DB PL RCT	3/10	A. Week 0, 2, 6, 10, 14, 3 mg kg ⁻¹ B. Week 0, 2, 6, 10, 14, 10 mg kg ⁻¹	21	7		6.2	7.7	> 0.05 (NS)

^aHalf of patients received only one infusion. CD, Crohn disease; DB, double blind; IR, infusion reaction; NS, not significant; pCD, paediatric CD; PL, placebo; Pso, psoriasis; RA, rheumatoid arthritis; RCT, randomized controlled trial; Retr, retrospective; S, significant.

Table 3 Formation of antibodies to infliximab (ATI) and infusion reactions with and without concomitant immunosuppressants

Reference	Level	Cohort	Study	Comparative groups	% ATI, group A	% ATI, group B	P-value	% IR, group A	% IR, group B	P-value
Augustsson <i>et al.</i> ³²	2B	n = 650, RA	Retr cohort	A. Comed prednisone 5 mg daily B. No comed				4.6	8.6	0.057 (NS)
Baert <i>et al.</i> ²³	2B	n = 125, CD	Prosp cohort	A. Comed with AZA 2.0–2.5 mg kg ⁻¹ daily or mercaptopurine 1.0–1.25 mg kg ⁻¹ daily or i.m. MTX 15 mg weekly B. No comed	RR 1	RR 2.4 RR 2.9	0.001			
Bendtzen <i>et al.</i> ³⁰	2B	n = 70, RA	Prosp cohort	A. Comed with MTX B. No comed	40	50	NS			
Colombel <i>et al.</i> ⁴²	2B	n = 500, CD	Retr cohort	A. Comed with AZA or MTX or a combination of these with corticosteroids, or corticosteroids alone B. No comed				3.7 (17/463)	5.4 (2/37)	
Crandall and Mackner ³¹	2B	n = 57, CD	Retr cohort	After two infusions infliximab: A. Comed with MTX, 6-mercaptopurine/AZA ≥ 4 months B. Comed with MTX, 6-mercaptopurine/AZA < 4 months After three infusions infliximab: A. Comed with MTX, 6-mercaptopurine/AZA ≥ 4 months B. Comed with MTX, 6-mercaptopurine/AZA < 4 months A. ≥ 3 months comed with prednisone ≥ 20 mg daily or MTX, 6-mercaptopurine/AZA B. No comed				11	60	S
Farrell <i>et al.</i> ²⁴	2B	n = 53, CD	Prosp cohort	A. ≥ 3 months comed with prednisone ≥ 20 mg daily or MTX, 6-mercaptopurine/AZA B. No comed	24	63	0.007 (S)	9.4	44	S
Hanauer <i>et al.</i> ²⁵	1B	n = 573, CD	DB PL RCT	Episodic infusions: A. Comed with MTX, 6-mercaptopurine/AZA or 5-aminosalicylates B. No comed Maintenance 5 mg kg ⁻¹ ; A. Comed with MTX, 6-mercaptopurine/AZA or 5-aminosalicylates B. No comed Maintenance 5–10 mg kg ⁻¹ ; A. Comed with MTX, 6-mercaptopurine/AZA or 5-aminosalicylates B. No comed	16	38	0.003 (S)	3	6	< 0.001 (S)
Jacobstein <i>et al.</i> ⁴¹	2B	n = 243, pCD	Retr cohort	A. Comed with MTX or 6-mercaptopurine/AZA B. No comed	7	11	0.42 (NS)	14.8	11.4	NS
Kinney <i>et al.</i> ⁴⁶	2B	n = 122, CD	Retr cohort	A. Comed with MTX B. No comed	4	8	0.42 (NS)	13	22.2	NS

Table 3 (Continued)

Reference	Level	Cohort	Study	Comparative groups	% ATI, group A	% ATI, group B	P-value	% IR, group A	% IR, group B	P-value
Maini <i>et al.</i> ⁴⁵	1B	n = 101, RA	DB PL RCT	Infliximab 1 mg kg ⁻¹ ; A. Comed MTX 7.5 mg weekly B. No comed Infliximab 3 mg kg ⁻¹ ; A. Comed MTX 7.5 mg weekly B. No comed	15	53				
				Infliximab 10 mg kg ⁻¹ ; A. Comed MTX 7.5 mg weekly B. No comed	0	7				
Miele <i>et al.</i> ³⁴	2B	n = 56, CD	Retr cohort	A. Comed MTX, 6-mercaptopurine/ AZA, ciclosporin B. No comed	28	83	0.02 (S)			
Vermeire <i>et al.</i> ²⁹	2B	n = 174, CD	Prosp cohort	A. Comed MTX or AZA B. No comed	44 (MTX)	73	0.002 (S)	16% (AZA/MTX) 14% (MTX)	40	0.04 (S)

AZA, azathioprine; CD, Crohn disease; comed, comedication; DB, double blind; i.m., intramuscular; IR, infusion reaction; MTX, methotrexate; NS, not significant; pCD, paediatric CD; PL, placebo; Prosp, prospective; RA, rheumatoid arthritis; RCT, randomized controlled trial; Retr, retrospective; RR, relative risk; S, significant.

Significant reduction of ATI formation was also achieved by comedication with prednisone ≥ 20 mg daily.²⁴ The risk of infusion reactions with concomitant prednisone 5 mg daily was reduced by 46.4% in 650 patients with RA who were retrospectively followed (not significant).³² On this subject patients with RA and those with psoriasis cannot be compared, as concomitant prednisone is not indicated for psoriasis. With continuous use of systemic corticosteroids in patients with psoriasis it should be considered that the severity of psoriasis can be influenced and rebound of psoriasis (more severe manifestations than ever before) can occur after its cessation.

Other studies on this subject have involved the use of several immunosuppressants together and therefore these results are less applicable here, as these therapeutic agents (except for methotrexate) are not used in patients with psoriasis (Table 3). Patients with RA and Crohn disease are frequently routinely treated with infliximab in combination with an immunosuppressant. Patients with psoriasis, however, are mostly treated with infliximab as monotherapy; a contraindication for the use of methotrexate is often one of the criteria to qualify for treatment with a biologic treatment. The presented results, however, encourage studies on the combination of (low-dose) methotrexate and infliximab for patients with psoriasis, to reduce the immunogenicity of infliximab, although the risk of overimmunosuppression may increase by such a combination.

Management of infusion reactions

No studies have been performed comparing several treatment strategies for handling infusion reactions to infliximab. The best available evidence is from descriptions of single cases^{11–13,15,16,28,31,33–38} and guidelines developed by infliximab-experienced specialists^{5,6,19,39,40}. The usual management of infusion reactions focuses on alleviating symptoms. In most cases an acute reaction is sufficiently treated by slowing the infusion rate, administering intravenous fluids and giving paracetamol and antihistamines. A complete treatment proposal is given in Figure 1. In a delayed infusion reaction administration of paracetamol, antihistamines and, if necessary, steroids is advised.

After an infusion reaction

Continuation of infliximab

After the occurrence of an infusion reaction it is often questioned whether the infliximab treatment can be continued. This depends on the severity of the reaction, the efficacy of treatment and possible treatment alternatives. After a serious infusion reaction the pros and cons of a new infusion should be especially deliberated. After a mild or moderate reaction there is usually no reason to stop infliximab treatment. Precautions can be taken to diminish the chance of a new infusion reaction. Among these precautions, desensitization, premedication and immunosuppressants as well as

adjustment of the schedule and dosage of infusions can be considered. These procedures will be described in more detail.

Premedication

Whether premedication could be more beneficial as secondary prophylaxis has been studied by Jacobstein *et al.*⁴¹ during infliximab treatment of 243 patients with Crohn disease. In this group, 28 patients developed an infusion reaction without premedication; of these, 36% were retreated with premedication, after which 20% developed a subsequent infusion reaction. No specific drugs and dosages are mentioned, only that they received antihistamines, antipyretics or corticosteroids. Forty-three per cent of the 28 patients were retreated without premedication, and of this group 50% developed a subsequent infusion reaction. This small group shows a trend towards a protective effect of premedication after an infusion reaction, although there was no statistical significance ($P = 0.5$).⁴¹ Colombel *et al.*⁴² re-treated 11 patients after an infusion reaction, of whom eight patients developed a subsequent infusion reaction despite premedication with 6-methylprednisolone, paracetamol and/or diphenhydramine.

Again, no solid evidence exists showing the prophylactic effect of premedication. However, it should be considered that giving premedication before an infusion might temper the severity of a potential infusion reaction and increase the chance of the completion of infusion. For instance, a regimen involving oral prednisolone 40 mg, an antihistamine and paracetamol 1000 mg 30 min before infusion is an option as secondary prophylaxis.

The number needed to treat (NNT) should be evaluated and could be favourable in case of reinfusion after an acute infusion reaction, considering the high incidence of subsequent reactions. If the NNT is calculated based on the study performed by Jacobstein *et al.*,⁴¹ 3.3 patients should be premedicated after an infusion reaction to prevent one subsequent infusion reaction. However, this study population is too small to result in a valid NNT.

As discussed in the 'prevention of infusion reactions' section, although low-risk therapeutic agents, the risk of potential side-effects should be evaluated and weighed against the additional value of the routine premedication.

Dosage

After an acute infusion reaction has occurred and the patient is to be re-treated, the next infusion should be started cautiously at a test dosage of 10 mL h^{-1} (100 mg mL^{-1}) and then slowly raised to a maximum of 125 mL h^{-1} .⁵ In case of a delayed infusion reaction Cheifetz and Mayer⁵ describe the tactic of increasing the dosage of infliximab to decrease the chance of a subsequent delayed infusion reaction. As previously stated, this reaction is probably caused by soluble antigen/antibody complexes. By increasing the dosage an antigen overload is created and the formation of soluble complexes

decreases. The same effect can be accomplished by reducing the interval between the infusions.⁵ A disadvantage of this strategy is the extra costs involved.

Desensitization

If continuation with infliximab after a severe infusion reaction is necessary, desensitization can be considered. Desensitization is a potentially dangerous procedure, which should be carried out only when treatment alternatives are absent. Patients with Crohn disease have successfully been desensitized for infliximab. In these cases special protocols were followed every time an infusion was given. The quantity of infliximab was divided and administered in decreasing dilutions^{10,18,43} (see the referred articles for exact procedures). Desensitization procedures should be carried out with the usual safety measures and performed by an experienced supervising physician with emergency equipment nearby.

Switching

If the decision is made to stop infliximab infusions despite all efforts to avoid infusion reactions, other biologics can be excellent alternatives, if infliximab was not already the last choice. For instance, switching from infliximab to adalimumab without complication has been described after the occurrence of an infusion reaction.^{16,44} The choice of a particular biologic, and what the interval should be, is dependent on the individual situation.

Conclusions

Although infusion reactions are in most cases not clinically severe, they can be a reason to stop infliximab treatment. Infliximab, however, is an effective therapy which is often started when only few alternatives are left. The therapy is usually chosen after a broad range of topical and other systemic therapeutic agents has been tried, which turned out to be unsatisfactory or to cause serious side-effects. Keeping this in mind, treatment discontinuation should be prevented if possible. We hope this guide can offer assistance in situations where discontinuation of infliximab treatment is undesirable and infusion reactions can be prevented or managed with relatively simple procedures.

Acknowledgments

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