Infliximab

Instructions for use

Table 1: Instructions for use (Infliximab)

Pre-treatment

100 % Agreement [1]

- Physicians are encouraged to enrol their patients in a registry (if available)
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- History focusing on prior exposure to treatments. History and clinical examination should focus on malignancies, infection, congestive heart failure, and neurological symptoms
- Recommended measures include:
    - Check for skin cancer
    - Check for lymphoadenopathy
    - Laboratory parameters (see **Table 2**)
    - Exclusion of tuberculosis (see chapter: “tuberculosis”)
    - Check for evidence of active infection
    - Check need for vaccinations
- Reliable contraception

During treatment

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/ Skindex-29 or -17)
- Clinical examination should focus on malignancies, risk factors for serious infections, congestive heart failure, and neurological symptoms
- Recommended measures include:
    - Check for skin cancer
    - Check for lymphadenopathy

- Laboratory parameters (see **Table 2**)

- Reliable contraception

Post-treatment

- After discontinuation of infliximab, patients should be followed up with medical history and physical examination

- For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter “wish for child / pregnancy”

[1] due to personal-financial conflict of interest 4 abstentions

Recommendations for lab controls

Table 2: Recommended laboratory controls (Infliximab)

	Period in weeks			
Parameter	**Pre-treatment**	**2**	**6**	**Thereafter, prior to each infusion**
Full blood count	x	x	x	x
Liver enzymes	x	x	x	x
Serum creatinine	x			
Urine status	x			
Pregnancy test (urine or blood)	x			
CRP	x	x	x	x
HBV/HCV	x			
HIV	x			
Interferon gamma release assay (TB exclusion)	x			
Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure.				
The recommendations are based on clinical experience. No evidence is available.				

Adverse drug reactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Key safety considerations for infliximab include common side effects (mainly infections and infusion reactions), as well as rare but important side effects, such as opportunistic infections, particularly tuberculosis. The relationship between infliximab and some other significant events that have been observed infrequently during treatment, including cases of severe liver toxicity, lymphoma or other malignancy, or congestive heart failure is less clear and therefore increased caution is recommended.

Infusion reactions

In clinical trials, infusion reactions (defined as any adverse event occurring during or within one hour after completion of the infusion) were the most common reasons for discontinuation of therapy. Infusion reactions were seen in approximately 18 % of infliximab-treated patients in phase III clinical trials vs approximately 5 % of patients receiving placebo. Most infusion reactions were mild to moderate, and included symptoms such as flushing, pruritus, fever or chills, headache, and urticaria. Severe infusion reactions, such as anaphylactic reactions, convulsions, erythematous rash and serum-sickness-like delayed-type hypersensitivity reactions (myalgia, arthralgia and/or exanthema occurring between one and 14 days after infusion) occurred in ~1 % of patients. One percent of infusions were accompanied by cardiopulmonary reactions, primarily chest pain, hypotension, hypertension or dyspnoea. Approximately 3 % of patients discontinued infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion.

If mild to moderate infusion reactions occur, treatment can usually be continued after decreasing the infusion rate or temporarily stopping the infusion. In these cases, pre-treatment with oral antihistamines, paracetamol/acetaminophen, and/or glucocorticosteroids should be considered for future infusions.

Infections

Infections are the most common serious adverse event described in spontaneous post-launch reports. Tuberculosis, bacterial infections (including sepsis and pneumonia), invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of > 5% include pneumocystis, candidiasis, listeriosis and aspergillosis. In all completed clinical trials with infliximab, 36.4 % of patients in the placebo groups (*n* = 1600; average weeks of follow-up: 29.0) and 52.0 % of patients in the infliximab groups (*n* = 5706; average weeks of follow-up: 45.5) experienced more than

one infection (Centocor, Inc. Data on file, Module 2.7.4 summary of clinical safety) (Psoriasis BLA, 2006; Pages 207, 209, 219). Serious infections were seen in 2 % of placebo-treated and in 4 % of infliximab-treated patients, the difference being due mainly to a higher rate of pneumonia and abscesses among patients receiving infliximab.

Antinuclear antibodies (ANA) and skin symptoms reminiscent of cutaneous lupus erythematosus

Approximately half of patients treated with infliximab may develop ANA that are frequently of transient nature. Anti-dsDNA antibodies were newly detected in approximately one-fifth of infliximab-treated patients compared with 0 % of placebo-treated patients. These autoantibodies are usually of low titre and mostly not associated with clinical symptoms. Treatment can be continued in patients with newly developed ANA without associated symptoms. The formation of autoantibodies has been associated in less than 1 % of cases with the onset of symptoms reminiscent of lupus erythematosus, which are almost always confined to the skin. In such patients it is recommended to discontinue infliximab treatment.

TNFi-induced paradoxical psoriasis

TNFi are effectively used in the field of inflammatory musculoskeletal, skin and bowel diseases. However, TNFi-induced cutaneous side effects are possible. Such 'paradoxical reactions' include the development of psoriasis, pustular psoriasis and psoriasiform lesions, reflecting an immunological paradox, as TNFi are used in the treatment of psoriasis. Psoriasis can be triggered in 1.5 – 5 % under the use of TNFi agents. In 52% of the cases the appearance is a palmoplantar pustulosis, in 49% a plaque type and in 15% a guttate-type. A potential mechanism could be the increase of the interferon alpha production. These psoriasiform lesions can be managed by topical or systemic anti-psoriatic-therapies and/or switch to another biologic agent, preferably from a different class. [1-3]

Table 3: Overview of important side effects

Very frequent	Injection-site reaction
Frequent	Infections
Occasional	Tuberculosis, reactivation of latent tuberculosis, heart failure
Rare	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases
Very rare	Autoantibodies, drug-induced lupus, malignancies

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Surgery

In the absence of controlled studies, the decision on how to manage TNFi therapy during surgery will be primarily based on individual factors such as activity of underlying disease, individual infection risk, reason for, type and risk of surgical procedure etc. While in many patients, minor surgical procedures may be carried out without interrupting TNFi therapy but with intensified prophylaxis and monitoring for pre- and peri-operative infections, treatment may be halted for some weeks in others. Elective surgery may best be placed between two infliximab infusions given at eight week intervals. In addition, an increased risk for infusion reaction may have to be considered when infusions are paused and restarted.

Infections

Monitoring measures during treatment should take into account that symptoms such as fever can be suppressed during TNFi therapy.

Combination of TNF antagonist and methotrexate

Treatment with TNFi and methotrexate can be combined. This may reduce the risk of formation of anti-drug antibodies [4]. This combination is particularly common for infliximab as the risk for the formation of anti-drug antibodies formation is highest. The combination may lead to an increased risk of infection, especially when compared to methotrexate monotherapy, but data are still scarce [5], see chapter: “Immunogenicity”.

Important contraindications

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

Absolute contraindications

- Active tuberculosis or other severe infections such as sepsis, and opportunistic infections
- Active chronic hepatitis B
- Congestive heart failure (NYHA class III/IV)
- Hypersensitivity to infliximab, murine proteins or any component of the formulation

Relative contraindications

- Pregnancy or breastfeeding
- Demyelinating diseases
- Latent tuberculosis
- History of recurrent or severe infections, localized infections, conditions predisposing to infections
- Patients living in geographical areas where tuberculosis and histoplasmosis are widespread
- Psoriasis patients with concomitant systemic lupus erythematosus or multiple sclerosis (MS)
- PUVA > 200 treatments (especially if followed by CsA use) – see chapter: "Cancer"
- Malignancies or lymphoproliferative disorders (see chapter malignancies)
- Hepatobiliary disorders

Drug interactions

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects:

There are no known interactions of infliximab with the metabolism of other drugs. The combination of infliximab with immunosuppressive drugs may enhance the risk of infection. [5] The combination with PUVA therapy might enhance the risk for skin cancer development.

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection.

References

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3. Melo FJ, Magina S. Clinical management of Anti-TNF-alpha-induced psoriasis or psoriasiform lesions in inflammatory bowel disease patients: a systematic review. *International journal of dermatology*. Dec 2018;57(12):1521-1532. doi:10.1111/ijd.14072
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