GUIDELINES FOR SCREENING, PROPHYLAXIS AND CRITICAL INFORMATION PRIOR TO INITIATING ANTI-TNF-ALPHA TREATMENT

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SUMMARY

These national clinical guidelines outlining the screening, prophylaxis and critical information required prior to initiating anti-TNF-alpha treatment have been approved by the Danish Society for Gastroenterology. Anti-TNF-alpha therapy is widely used in gastroenterology (for inflammatory bowel disease), rheumatology (for rheumatoid arthritis, psoriatic arthritis and spondyloarthropathies) and dermatology (for psoriasis).

With this background, the Danish Society for Gastroenterology established a group of experts to assess evidence for actions recommended before treatment with anti-TNF-alpha agents.

Screening should take place for both active tuberculosis and latent tuberculosis. Screening must evaluate the risk of hepatitis B exposure/infection and that of other viral infections such as human immunodeficiency virus (HIV) and varicella zoster virus (VZV). The assessment should include a history of previous malignancies (cases of malignant disease within 5 years of anti-TNF-alpha treatment should be carefully considered). The physical examination should include lung/heart auscultation and lymph node examination, and the paraclinical investigations should include chest X-rays and laboratory tests, including an interferon gamma release assay, a hepatitis B test, an HIV test and, when prior VZV infection is uncertain, a VZV antibody test.

Prophylaxis: Isoniazid should be administered in cases of suspected latent TB infection. Antiviral treatment is recommended in HBsAg-positive patients at the start of anti-TNF-alpha treatment. Before anti-TNF-alpha therapy, vaccination with 23-valent pneumococcal vaccine is recommended, and HBV vaccination may be considered in seronegative patients. Annual vaccination against seasonal influenza is recommended. Human papilloma virus vaccination should be administered in accordance with the guidelines of the National Board of Health of Denmark. In patients without a prior VZV infection, VZV vaccination may be considered.

Information for patients: Anti-TNF-alpha treatment results in a generally increased risk of infection and latent tuberculosis flare-up. Women are advised to comply with the national guidelines for screening for cervical cancer, and their HPV immunisation status should be clarified. An increased risk of lymphoma with biological therapy in combination with thiopurines should be mentioned. Patients are advised to seek medical advice in case of herpes zoster infection.

A checklist for use before anti-TNF-alpha therapy is provided (Table 4).

DELIMITATION OF THE SUBJECT

Based on the frequency with which anti-TNF-alpha therapy is used in gastroenterology, this guideline is limited to drugs with this mode of action (infliximab and adalimumab). Etanercept is mentioned in a few places because of its use in rheumatology and dermatology.

For a variety of other immunomodulators, including azathioprine, 6-mercaptopurine and methotrexate, similar considerations apply, and these principles can also be used for treatment with these drugs. The evidence for this applicability falls outside of these guidelines. In every case, special precautions associated with each of these drugs should be assessed before starting treatment.

INTRODUCTION

For more than 10 years, chronic inflammatory diseases have been increasingly treated with biological drugs —particularly with anti-TNF-alpha agents. Anti-TNF-alpha in combination with immunosuppressive therapy, mainly azathioprine, 6-mercaptopurine and methotrexate, are used in an increasing number of patients. This use increases the risk of opportunistic infections. These infections are often difficult to diagnose and are associated with significant morbidity and potentially fatal outcomes. Against this background, it is recommended that patients be screened for possible latent infections before starting therapy.

At the end of 2009, the Danish Society for Gastroenterology convened a group of experts to assess the evidence for actions recommended before treatment with anti-TNF-alpha, mainly in patients with inflammatory bowel diseases — ulcerative colitis and Crohn's disease.

Anti-TNF-alpha is widely used in gastroenterology (for inflammatory bowel disease), rheumatology (for rheumatoid arthritis, psoriatic arthritis and spondyloarthritis) and dermatology (for psoriasis). With this background, the group's coordinator found it desirable for the different specialties to establish a joint recommendation for screening before starting anti-TNF-alpha therapy, and for the guideline to gain approval from infectious disease societies.

These recommendations refer to the treatment type and not to any particular disease.

Guidelines for the screening and prevention of TB before the start of anti-TNF-alpha therapy, with much more background information, can be found on various scientific societies' Web sites (http://www.dsinfm.dk/), and the present recommendations do not differ significantly from those guidelines.

DEFINITIONS:

Infections related to treatment with anti-TNF-alpha are classified into 5 groups:

1. Tuberculosis (TB);

2. Human papilloma virus (HPV);

3. Hepatitis B and C;

4. Varicella zoster virus (VZV), Herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein Barr virus (EBV) and human immunodeficiency virus (HIV);

5. Other infections.

Because of their clinical significance, this guideline also covers previous cancerous diseases and heart failure.

ABBREVIATIONS

CI: 95% confidence limits

IBD: Inflammatory bowel disease

IFN-γ: Interferon gamma

IGRA: Interferon gamma release assay

LTBI: Latent TB infection

MTB: *Mycobacterium tuberculosis*

RA: Rheumatoid arthritis

TB: Tuberculosis

TST: Tuberculin skin test

METHODS

Literature searches were undertaken on February 1, 2010. The searches were performed using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) and the Cochrane Library (http://www.thecochranelibrary.com) with keywords and Medical Subject Headings (MeSH) that included *tumour necrosis factor inhibitors, herpes simplex virus or HSV, cytomegalovirus or CMV, human papilloma virus or HPV, varicella or zoster, human immunodeficiency virus or HIV, opportunistic infection, review inflammatory bowel disease, tumour necrosis factor-alpha/analysis / * antagonists & inhibitors, adverse effects, guidelines, pregnancy, heart failure, neoplasm, safety, vaccination, infliximab, adalimumab, certolizumab, pneumonia, Clostridium difficile* and *Streptococcus pneumoniae* and with the following limits: *species* (human) and *languages* (English).

Table 1 shows the types of evidence, evidence levels and recommendations used. Table 2 is a Quick Guide and table 3 shows the testimonials.

TOPIC SPLIT REVIEWS

Mycobacterium tuberculosis

Risk of tuberculosis during treatment with anti-TNF-alpha

Tuberculosis (TB) is caused by the bacterium *Mycobacterium tuberculosis* (MTB). Transmission occurs when a person with pulmonary TB coughs or sneezes, producing infectious aerosol. Of those people infected, 10% develop active TB. The remaining 90%

will develop latent TB, which normally causes no symptoms. Persons with latent TB infections, however, may progress to active TB [1] when there is an imbalance in immunological control, which can be caused by malnutrition, aging, HIV infection and now also by treatment with immunosuppressive drugs such as anti-TNF-alpha agents[2-4].

TUBERCULOSIS AND ANTI-TNF-ALPHA IN DENMARK

Anti-TNF-alpha treatment increases the risk of latent TB reactivation. In Denmark, in the period 2002-2009, the Danish Medicine Agency received reports of 15 cases of TB that had occurred after anti-TNF-alpha treatment (12 cases of MTB, one case of *M. bovis*, one case of *M. avium* and one case of *M. marinum*). Two cases occurred in patients with Mb. Crohn, four in patients with Mb. Bechterew, eight in patients with arthritis, including one with psoriatic arthritis, and one in a patient with an unknown disease. Nine patients received infliximab, four received adalimumab, one received etanercept and one received all three drugs (Report by Pernille Chantal Canci Pedersen, Danish Medicine Agency, in February 2010).

Approximately 6.000 patients have received anti-TNF-alpha treatment in Denmark over the past 10 years. With 15 reported cases of TB, this rate (15/6000/10 years) corresponds to an incidence of 25/100.000/year. Comparing this figure with the incidence of 6.7/100 000 per year we see for TB cases in Denmark (http://www.ssi.dk/) reveals that treatment with anti-TNF-alpha entails a nearly 4-fold greater risk. A study from Sweden in 2008 reported an almost 4-fold increase in risk, with 13 cases of TB in patients treated with anti-TNF-alpha [5]. Because not all cases are reported, one suspects that the incidence is actually higher.

In selected groups, prophylactic treatment decreases the risk of subsequent TB development [6]. There has been a marked reduction in the number of new TB cases since the introduction of screening and preventive treatment before anti-TNF-alpha therapy [7]. There have been, however, no randomised trials in patients prior to commencement of anti-TNF-alpha treatment, although it is easy to extrapolate the data from the above studies to patients who need anti-TNF-alpha therapy.

We recommend that all patients be screened for LTBI before anti-TNF-alpha treatment and that preventive treatment be initiated in all patients in whom there is a suspicion of latent TB infection. Anti-TNF-alpha therapy can be started after 1 month of preventive treatment.

SCREENING FOR LATENT TB

There are no 100% specific or 100% sensitive methods for diagnosing latent TB infection, and with the currently available methods, one cannot predict with certainty which patients will develop active TB during anti-TNF-alpha therapy.

RISK FACTORS FOR LTBI:

People who have had prolonged stays in high TB incidence areas for > 3 months, have been in close contact with patients with infectious TB, demonstrate radiological evidence of previous TB infection or have undergone previous treatment for active TB or LTBI are considered to be at risk.

DIAGNOSIS OF LTBI:

The Mantoux test (tuberculin skin test) has now been replaced by the new interferon gamma release assay (IGRA) in the form of QuantiFERON TB-Gold In-Tube (QFT-GIT) and T.SPOT- TB for the identification of persons who may be infected with MTB. The IGRA test is highly specific for MTB, and in practice, there are no "false positive" results, as with the Mantoux test. The IGRA test is more sensitive than the Mantoux, especially among immunosuppressed patients (fewer false negatives) [8]. In contrast to the Mantoux test, there is a built-in positive control, which allows the distinction of true negatives from false negatives, which otherwise would be inconclusive.

Neither an IGRA test nor Mantoux can distinguish between active TB and LTBI.

What do we know about IGRA testing among candidates for anti-TNF-alpha treatment in Denmark?

In light of a recent study in Denmark (11), it can be assumed that approximately 5-7% of patients with rheumatic disorders in Denmark should be offered preventive treatment on the basis of a positive IGRA test. In addition, others should be offered preventive treatment in light of other risk factors. Fewer IBD patients will need preventive treatment because this population is younger and less likely to come from an area that is highly endemic for TB.

Based on indirect evidence and extrapolation from Mantoux test studies, patients should be screened for LTBI by assessment of risk factors and chest X-rays. IGRA testing is recommended as the best indirect test for LTBI. The Mantoux test is recommended only in cases in which the IGRA test cannot be performed.

Treatment with prednisolone and other immunosuppressive drugs may affect the outcome of IGRA testing

There is an increased incidence of indeterminate IGRA test results in persons receiving immunosuppressive therapy with prednisolone [2,9-11], and there have been several inconclusive results in patients taking concomitant medications [9-10]. It is conceivable that IGRA testing has a lower sensitivity if performed while the patient is receiving an immunosuppressive medication such as prednisolone, azathioprine, 6-mercaptopurine, methotrexate or anti-TNF-alpha.

It is recommended that IGRA testing be performed in patients before treatment with immunosuppressive drugs to avoid inconclusive and possible false negative results. If a patient on predni-

solone (or another immunosuppressive therapy) has a negative or inconclusive IGRA result, then other risk factors should be examined thoroughly.

ACUTE NEED FOR ANTI-TNF-ALPHA THERAPY

In certain cases of severe active IBD, surgery might be prevented by immediately starting anti-TNF-alpha therapy. In these cases, one might prioritise the patient's disease over the response to immunological testing. Such patients should be screened with a thorough assessment of risk factors for active TB and LTBI, a chest X-ray should be performed and an IGRA test or Mantoux test should be performed. If there is uncertainty about whether there is a medical history or radiological suspicion of LTBI, TB prophylaxis must be initiated, and the patient should be conferred with infectious disease and pulmonary disease specialists.

If subsequently there is a positive Mantoux test or a positive IGRA test, the patient must continue/begin medical TB prophylaxis and be regularly assessed for possible signs of TB reactivation.

If presenting a negative IGRA test (or Mantoux test), negative history and a normal chest X-ray, the patient should be assessed regularly for signs of reactivation because our screening is not 100% sensitive. The IGRA testing might be repeated.

Referral/conferral with infectious disease or lung disease departments for prophylactic treatment:

• Immigrants from highly endemic areas (incidence of 50/100.000)

• Prolonged travel (> 3 months duration) in a highly endemic area and contact with the local population

• Previous contact with infected patients

• Positive IGRA test

• Positive Mantoux test (> 12 mm in BCG vaccinated or > 6 mm in unvaccinated)

• TB-suspicious chest X-ray and no suspicion of active TB

***Refer also in the following cases*:**

• Active TB is suspected

• Previously treated for active TB or LTBI

• Suspicion of false negative IGRA test or Mantoux test

• Indeterminate IGRA test + risk factors

Human papilloma virus (HPV)

HPV, particularly types 16 and 18, is a prerequisite for the development of cervical cancer and premalignant stages [12,13]. Women aged 23-65 years old should be screened for cervical cancer every 3 to 5 years. Other anogenital cancers have weaker associations with HPV infection. HPV types 6 and 11 result in warts, and common warts are associated with other HPV types. Finally, larynx papillomas are frequently caused by infection with HPV types 6 and 11. With immunosuppression, be it due to organ transplantation or HIV infection, the incidence of HPV-associated cancers increases [14]. In the same patients, there is an increased risk of warts, which are difficult to treat. Despite this risk, HPV infections have not been demonstrated to occur more frequently in the skin or cervix of immunosuppressed women after renal transplantation [15].

The effect of anti-TNF-alpha treatment on HPV-associated diseases is unclear. There have been a few reports of treatment with infliximab and etanercept exacerbating existing anogenital warts [16], but neither randomised clinical studies nor patient registries provide evidence for increased incidence of cutaneous HPV infection or HPV-associated cancers [17-19].

Bivalent HPV vaccines protect against high-risk HPV types 16 and 18, whereas quadrivalent HPV vaccines are also directed against types 6 and 11 and thus protect against genital warts. HPV vaccines provide significant protection for immunocompetent individuals [20,21]. HPV vaccines are approved for female patients aged 9-26 years old and are recommended in Denmark for 12- to 16-year-old girls. In the United States, where HPV vaccination is recommended up to 26 years of age, the same recommendations are applied for immunosuppressed patients [22]. The immune response to HPV vaccination is impaired in HIV-positive patients and in smokers [23]. It is not known whether patients receiving anti-TNF-alpha therapy have an altered response to HPV vaccination.

HEPATITIS B AND C

Hepatitis B

Hepatitis B has a prevalence of 0.3% in Denmark. Persons born in other countries have higher incidences, with a very high incidence in east Asia.

A Spanish multicentre study recently showed that the prevalence of HBV infection in IBD patients is equivalent to that in the background population [24].

Data from HBsAg-positive cancer patients indicate that reactivation of HBV replication occurs in 20-50% of patients receiving immunosuppressive therapy or cancer chemotherapy [25].

The influence of anti-TNF-alpha treatment on HBV infection in patients with IBD has not been studied. However, there has been a growing number of case reports describing HBV reactivation during treatment with anti-TNF-alpha. The clinical course is highly variable, possibly leading to acute, fulminant liver failure. Most

cases have been reported in HBsAg-positive patients, but there have also been cases of patients who are HBsAg-negative and only anti-HBc-positive [26-28].

HBsAg-positive patients and patients with a chronic active HBV infection should be referred to a specialist unit and treated with prophylactic antiviral therapy at the beginning of their anti-TNF-alpha therapy. Significantly increased transaminase levels may be an appropriate indicator for initiating treatment before anti-TNF-alpha therapy, but it must depend on a specific assessment of the two diseases. Prophylactic treatment prevents reactivation.

HBV vaccination should be considered in all HBV-seronegative patients, and it is recommended in risk groups according to the guidelines of the National Board of Health of Denmark. The efficacy of vaccinations may be reduced because of treatment with anti-TNF-alpha; thus, serological responses should be measured after the vaccination is completed.

HEPATITIS C

In northern Europe and the United States, it is estimated that 0.2-2% of the population is infected with HCV, whereas in southern Europe, the prevalence is somewhat higher (3-5%). TNF-alpha's role in the regulation and replication of HCV infection is unclear, but anti-TNF-alpha therapy may have a positive impact on HCV infection. However, no improvement was found with anti-TNF-alpha therapy in rheumatoid arthritis patients with HCV [29]. IBD patients with HCV can be treated with anti-TNF-alpha, and IBD patients do not need to be screened for HCV before treatment.

VARICELLA ZOSTER VIRUS (VZV)

Varicella zoster virus (VZV) causes two different disease courses: the primary infection, chicken pox/varicella; and shingles/herpes zoster (HZ), a reactivation of latent VZV. Chicken pox is a childhood disease that 90-95% of patients will develop by 12 years of age. In Sweden, it has been documented that 98% of 20-30-year-olds have antibodies to VZV. Former infection can be determined by the measurement of VZV IgG antibodies. Reactivation of VZV occurs at all ages but mainly in the elderly and immunocompromised. The severity of symptoms increase with age, in the presence of other diseases and with immunosuppressive therapy, including glucocorticoids, which also increases the risk of dissemination and the complications of reactivation.

Herpes zoster is one of the most common adverse reactions reported in clinical studies with anti-TNF-alpha therapy. Serious and fatal infections have been described.

Immunisation against primary varicella and reactivation (in HZ) is possible with vaccine containing live, attenuated VZV [30]. In subjects over 60 years old, vaccination reduces the incidence of herpes zoster by 50% and the risk of postherpetic neuralgia by 66% [30]. The vaccine, a live, attenuated vaccine that is not identical to the vaccine marketed for primary immunisation, is contraindicated in patients with impaired cellular immune response and is not recommended in patients receiving immunosuppressive therapy or anti-TNF-alpha treatment. The vaccine is expected to be marketed in Denmark but until then, unless multiple studies demonstrate otherwise, it will be contraindicated in many candidates for anti-TNF-alpha therapy.

The ECCO (European Crohn's and Colitis Organisation) guidelines recommend vaccination for non-immunised immunocompetent patients prior to treatment with immunosuppressive drugs [31]. The American College of Rheumatology recommends vaccinating all RA patients aged ≥ 60 years old, even if they receive MTX or low-dose steroids.

HERPES SIMPLEX VIRUS (HSV)

Primary infection with herpes simplex virus (HSV) in immunocompetent individuals often results in an asymptomatic to mild and self-limiting oro-labial (HSV Type 1) or genital (HSV type 2) HSV infection. Immunocompromised patients are at greater risk for a disseminated infection. There have been three case reports on the development of HSV encephalitis (one patient treated with infliximab and two patients treated with adalimumab). Severe, widespread, cutaneous HSV infection has also been described in a patient treated with infliximab. There is no vaccine against HSV infection.

CYTOMEGALOVIRUS (CMV)

Most cytomegalovirus (CMV) infections are asymptomatic, but it can present as a mononucleosis-like disease. CMV reactivation may occur during immunosuppressive therapy, but it is often asymptomatic [31]. In a study of 15 RA patients who started treatment with infliximab and who were followed up for 6 weeks, no signs of CMV reactivation were found [32]. There have been several reports of CMV infection as a complication with infliximab therapy, in which CMV infection first appeared after several months of treatment. There is no marketed vaccine against CMV in Denmark.

Screening for latent or subclinical CMV infection is not necessary before starting anti-TNF-alpha therapy.

EPSTEIN-BARR VIRUS (EBV)

Epstein-Barr virus (EBV), human herpesvirus-4, is a very common viral infection, and as many as 90-95% of people will have had the infection before 35-40 years of age. After primary infection with EBV, the virus persists in circulating B-lymphocytes. Apart from mononucleosis, EBV is associated with Burkitt's lymphoma and nasopharynx-pharyngeal carcinoma. In 15 infliximab-treated RA patients, no evidence of reactivation of EBV was found, but the follow-up was only 6 weeks [32]. There are case reports associating biological treatment with the onset of EBV infection. There is, however, no vaccine against EBV.

Screening for latent or subclinical EBV infection is not necessary prior to starting anti-TNF-alpha therapy.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Tumour necrosis factor participates in the pathogenesis of HIV infection by increasing the cellular spread of the virus and by stimulating viral replication. Blockade of circulating TNF could therefore be a therapeutic option, although it has been tried with no effects on HIV replication. The safety of treating HIV patients with anti-TNF-alpha agents is largely derived from case reports [32]. In a recent study, eight HIV patients with various rheumatic diseases were treated with etanercept and followed for 28 months. All patients had CD4 cell counts > 200 m/l, no co-infection and an HIV viral load of < 60,000 copies/mm^3[33]. Five patients received concomitant HAART (highly active antiretroviral therapy) treatment, and neither opportunistic infections nor increased viral replication was observed during treatment. A good effect of treatment was recorded in seven patients, but due to later suboptimal efficacy, four patients were switched to infliximab or adalimumab.

INFLUENZA VIRUS

No data currently exist on the incidence of influenza infection in IBD patients, but the use of immunosuppressive drugs increases the risk of infection. Annual vaccination against seasonal influenza decreases the risk of infection, and vaccination is recommended for all. There is no evidence of a reduced response to the vaccine during treatment with immunosuppressive drugs [31]. The National Board of Health's general guideline regarding influenza should be followed.

OTHER BACTERIAL AND PARASITIC INFECTIONS AND FUNGAL INFECTIONS

Other bacterial infections are limited to *Streptococcus pneumoniae*, *Salmonella* spp., *Clostridium difficile*, *Legionella pneumophila*, *Listeria monocytogenes* and *Nocardia* spp.

Bacterial pneumonia is one of the most common opportunistic infections in patients receiving anti-TNF-alpha treatment. These patients are considered to be at high risk for infection with *Streptococcus pneumoniae* in general [34-35], and invasive pneumococcal infections have been observed during treatment. In an investigation from the Mayo Clinic of 500 consecutive patients treated with infliximab, bacterial pneumonia was found in eight patients, two of whom had lethal courses. *Streptococcus pneumoniae* was isolated in one patient [35].

A 23-valent pneumococcal vaccine is recommended for all patients before starting treatment with anti-TNF-alpha, as therapy can reduce antibody formation and immunity [31]. It is recommended that the vaccine be repeated every 3-5 years (http://www.cdc.gov/mmwr/pdf/rr/rr4608.pdf).

IBD patients treated with anti-TNF-alpha agents are at risk for severe *Salmonella enteritidis* and *Salmonella typhimurium* infections. Bacterial gastroenteritis can simulate activity in IBD, and upon suspicion of acute gastroenteritis, the patient's faeces should be cultured for pathogenic enteric bacteria, including *Salmonella* spp., before the initiation of anti-TNF-alpha treatment.

The incidence of infection with *Clostridium difficile* (CDAD — *C. difficile*-associated disease) has significantly increased in U.S. patients with IBD and colon involvement [37]. This increase has also been observed in several European countries. Concomitant IBD and CDAD lead to increased need for hospitalisation, prolonged hospitalisation and a four-fold increase in mortality. Data on IBD patients with CDAD being treated with anti-TNF-alpha agents are scarce. A single study has shown a significantly increased risk of CDAD in IBD patients treated with immunosuppressive drugs other than anti-TNF-alpha agents [37]. It is recommended the faeces of all IBD patients be examined for *Clostridium difficile* upon suspicion of disease activity. The examination should include both cytotoxins A and B.

It is generally recommended that all IBD patients be examined for enteropathogenic bacteria for differential diagnostic reasons.

Patients treated with anti-TNF-alpha have a higher risk of infection with *Listeria monocytogenes*, *Nocardia* spp. and *Legionella pneumophila*. These diseases are not latent and cannot be reactivated by anti-TNF-alpha treatment. Screening is not recommended prior to treatment.

Fungal and parasitic infections are limited to *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Histoplasma capsulatum, Pneumocystis jiroveci* (*P. carinii*), *Toxoplasma gondii* and *Strongyloides stercoralis*.

Most of the data on these opportunistic infections has originated from case reports. Therefore, it is not currently possible to reliably specify the risk for these infections during anti-TNF-alpha treatment [31]. Of the opportunistic infections, it appears that localised infections with *Candida* spp. are by far the most common.

A general screen for fungal and parasitic infections is not recommended prior to treatment with anti-TNF-alpha. Patients residing in endemic areas or with a prior fungal or parasitic infection must be assessed individually and may be conferred with an infectious disease specialist.

JC VIRUS

Infection and development of progressive multifocal leukoencephalopathy (PML) has occurred during treatment with natalizumab (Tysabri®) and with a number of other immunosuppressive therapies but not with anti-TNF-alpha therapy.

CANCER

Cancer in general

There appears to be no increased risk of malignancy with anti-TNF-alpha therapy (infliximab) *per se*. A meta-analysis of 21 placebo-controlled, randomised trials (5356 patients) in Crohn's

disease and with cohorts undergoing long follow-ups [3,38-39] showed no increase in the number of patients with cancerous diseases. Adalimumab treatment of 19041 patients with a number of autoimmune diseases (including Crohn's disease) also showed no increase in the frequency of malignancy in a meta-analysis of 36 controlled clinical trials [2].

LYMPHOMA

It is uncertain whether anti-TNF-alpha treatment alone increases the incidence of lymphoma. In a meta-analysis of 26 studies (8905 patients with Crohn's disease: 9 clinically controlled trials, 3 cohort studies and 14 consecutive case studies) with infliximab, adalimumab and certolizumab, 13 cases of non-Hodgkin lymphoma occurred [40], but 11 of these patients were being or had been treated with other immunosuppressive therapies (thiopurines/methotrexate). Overall, the lymphoma risk was 6.1 per 10000 patient-years versus an expected lymphoma risk of 1.9 per 10000 patient-years (data from the Surveillance, Epidemiology and End Results [SEER] registry). The standardised incidence ratio (SIR) was 3.2 (95% confidence limits [CI]: 1.5 to 6.9). When disaggregated by sex and age, SIR was statistically significantly elevated (SIR: 5.9 [CI: 1.3 to 18.1]) only for men between 20 and 54 years old.

Monotherapy with thiopurines increases the risk of lymphoma among patients with IBD, with a relative risk increase of 4 to 5 in thiopurine patients versus those patients who have never received thiopurines [41 -42].

The incidence of a rare type of lymphoma with very high mortality (hepatosplenic T-cell lymphoma) is currently increasing, especially among younger men receiving anti-TNF-alpha therapy — often combined with other immunosuppressives, particularly thiopurines [43-46]. However, hepatosplenic T-cell lymphoma has also been found in anti-TNF-naïve patients treated with thiopurines [46].

The incidence of lymphoma is elevated in rheumatoid arthritis (RA) and is associated with high disease activity [46,47]. The risk of lymphoma is 2- to 5-fold higher in RA patients than in the general population [49-51], and a similar risk has been observed in RA patients receiving anti-TNF-alpha [47,50, 52]

A meta-analysis from 2006 reported a higher incidence of malignancies in patients treated with infliximab and adalimumab [53]. Patients treated with etanercept were not included in that meta-analysis. In a study of patients with Wegener's granulomatosis treated with etanercept plus cyclophosphamide or cyclophosphamide plus placebo, an increased incidence of solid tumours was found relative to the cyclophosphamide/placebo group. [54]

CERVICAL CANCER/DYSPLASIA

There is no evidence for an overall increased incidence of abnormal cervical smears or cervical cancer among women with chronic inflammatory bowel disease [55-57]. There seems to be a slightly increased risk [56] of cervical cancer among women who have received combined glucocorticoids and thiopurine treatment (odds ratio, 1.4; CI: 1.2 to 1.8). See additional information under HPV.

PREGNANCY AND LACTATION

Infliximab and adalimumab are classified by the Food and Drug Administration (FDA) as class B substances during pregnancy (animal studies have shown no foetal risk, but there have been no controlled human studies). The administration of anti-TNF-alpha treatment during pregnancy and breastfeeding will be addressed in a future guideline.

HEART FAILURE

Anti-TNF-alpha therapy (infliximab) was evaluated versus placebo in a randomised, controlled clinical trial of stable chronic heart failure (New York Heart Association [NYHA] classes III and IV) with a left ventricular ejection fraction [EC] ≤ 0.35. The group receiving infliximab infusions (10 mg/kg body weight) had increased mortality [58]. No increase in the risk of developing heart failure was observed during anti-TNF-alpha therapy (infliximab, adalimumab) in patients with either rheumatoid arthritis or Crohn's disease [59].

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Table 1 Evidence level for investigations and recommendations

Type of evidence	Evidence level	Recommendation
Randomised, controlled clinical trials (therapeutic or diagnostic) and meta-analyses of randomised, controlled clinical trials or systematic reviews	I	A
Prospective and controlled but non-randomised investigations (cohort studies); diagnostic testing evaluated by direct methods	II	B
Studies that are controlled but not prospective (case-control studies); diagnostic testing evaluated by indirect methods	III	
Descriptive studies, expert opinions and narrative reviews	IV	C

Table 2 Quick guide

SCREENING	
Tuberculosis	• Suspicion of active tuberculosis (TB) 1. Focus on general and focal symptoms (e.g., prolonged fever, weight loss, cough, swollen lymph nodes or unexplained illness) • Suspicion of latent TB infection (LTBI) 1. Exposure to possible infection sources 2. Previous contact with an infected patient; immigrants from highly endemic areas 3. Prolonged stay in and travel to endemic TB areas 4. Former TB or preventive treatment for TB
Other diseases	• Previous malignancy 1. If malignant disease within 5 years, anti-TNF-alpha treatment (and combination therapy with other immunosuppressive therapies) should be carefully considered, with possible conferral with an oncologist. • Former varicella or herpes zoster infection • Risk of hepatitis B exposure/infection • Heart failure 1. On suspicion, confer with a cardiologist and have echocardiography performed.
Assessment	• Physical examination 1. Lung and heart auscultation 2. Lymph node examination for glandular enlargement 3. Global assessment regarding general condition • Chest X-rays assessing active or prior TB • Laboratory tests 1. Interferon gamma release assay (IGRA) test (if IGRA testing is not possible, a tuberculin skin test should be performed) 2. Hepatitis B test: Test for HBsAg, anti-HBs and anti-HBc. If HBsAg or anti-HBc is positive, then test for HBV-DNA and HBeAg. 3. Human immunodeficiency virus (HIV) test 4. Varicella zoster virus (VZV) test: If prior VZV infection is uncertain, measure VZV antibody concentration in immunocompetent patients.
PROPHYLAXIS	
Vaccinations	• Human papilloma virus (HPV) vaccination is recommended for women in accordance with the guidelines of the National Board of Health of Denmark. • VZV vaccination may be considered if the patient does not have a history of varicella or herpes zoster infection, their VZV antibodies are negative and they are immunocompetent. • Vaccination with the 23-valent pneumococcal vaccine is recommended before anti-TNF-alpha treatment and every 3 to 5 years thereafter. • HBV vaccination may be considered in seronegative patients and especially in patients at risk. • Annual vaccination against seasonal influenza is recommended in accordance with the guidelines of the National Board of Health of Denmark. • The patient should be queried regarding possible vaccination with a live vaccine within the last 3 months.
Other prophylaxis	• Prophylaxis with isoniazid in cases of suspected latent TB infection • HBsAg-positive patients are advised to receive antiviral treatment at the start of anti-TNF-alpha therapy.
INFORMATION FOR PATIENTS	
	• Anti-TNF-alpha therapy entails an overall increased risk of infection. • Anti-TNF-alpha therapy increases the risk that a latent tuberculosis infection will flare up and cause illness. If latent tuberculosis is suspected, preventive treatment is recommended. • Latent TB is not contagious because the bacteria are encapsulated, and there are few live bacteria. • The increased risk of lymphoma in combination therapy involving biologicals with other immunosuppressives (particularly thiopurines) should be mentioned. • Women are advised to comply with the national guidelines regarding cervical cancer screening. • The patient's human papilloma virus (HPV) immunisation status should be clarified. • Patients are encouraged to seek medical advice if there are signs of herpes zoster for early treatment initiation.

Table 3 Levels of evidence for clinical recommendations

Testimonials	**Level of evidence/ Recommendations**
Tuberculosis	
• There is a markedly increased risk of TB infection reactivation during anti-TNF-alpha treatment, and patients with LTBI should be given preventive treatment before starting anti-TNF-alpha therapy.	II-III / B
• IGRA tests are more sensitive than tuberculin skin tests and are therefore recommended.	
• Treatment with prednisone and other immunosuppressive drugs can lead to inconclusive and possibly false negative IGRA test (and Mantoux test) results. When negative or inconclusive results occur, other risk factors should be assessed.	II-III / C II-III / C
• An IGRA test (or tuberculin skin test) is recommended before starting treatment with immunosuppressive agents.	IV / C
Human papilloma virus (HPV)	
• Women should be screened for cervical cancer according to the guidelines of the National Board of Health of Denmark.	IV / C
• •HPV vaccination is recommended for women according to the guidelines of the National Board of Health of Denmark.	IV / C
Hepatitis B and C	
• All patients should be tested for hepatitis B with HBsAg, anti-HBs and anti-HBc before beginning treatment. If HBsAg- or anti-HBc positive, further investigations should be undertaken, including HBV-DNA and HBeAg.	IV / C
• HBV vaccination may be considered in seronegative patients and is recommended in patients at risk.	IIIb / C
• HBsAg-positive patients should receive prophylactic antiviral therapy with nucleoside analogues at the start of anti-TNF-alpha therapy.	IV / C
• HBV reactivation can occur in HBsAg-negative and anti-HBc-positive patients, but routine prophylaxis is not recommended. However, control of HBV-DNA every half-year and attention to liver enzyme increases are recommended.	IV / C
• Patients should not be tested for hepatitis C.	IV / C
Varicella zoster virus (VZV) - herpes simplex virus (HSV) - cytomegalovirus (CMV) Epstein Barr virus (EBV) - human immunodeficiency virus (HIV) - influenza virus	
• Testing for latent or subclinical cytomegalovirus (CMV) infection before starting anti-TNF-alpha therapy is not indicated.	II / B
• Testing for latent herpes simplex infection (HSV) before anti-TNF-alpha therapy is not indicated.	II / B
• Testing for latent or subclinical Epstein Barr virus (EBV) before anti-TNF-alpha therapy is not indicated.	IIa / B
• If the patient has not had a varicella/herpes zoster virus infection or has been vaccinated against chicken pox, then measurement of VZV antibodies and VZV vaccination prior to anti-TNF-alpha therapy may be indicated.	IV / B
• Patients should be questioned about their risk factors for HIV infection. Testing for HIV infection may be considered before treatment with anti-TNF-alpha.	IV / C
• Annual vaccination against seasonal influenza is recommended in accordance with the guidelines of the National Board of Health of Denmark.	II / B
Other infections	
•Vaccination with 23-valent pneumococcal vaccine is recommended prior to treatment with anti-TNF-alpha and every 3-5 years thereafter.	IV / C
•Faecal investigation for pathogenic bacteria is recommended in IBD patients before initiating anti-TNF-alpha treatment.	IV /C
- Including Clostridium difficile	II / B
- Including testing for cytotoxins A + B	II / B
• There is no indication for screening for other bacterial or parasitic infections mentioned in the text or for fungal infections prior to anti-TNF-alpha treatment.	IV / C
Cancer	
• Before anti-TNF-alpha treatment, questions about previous malignancies are mandatory. In cases of malignancy within 5 years, biological treatment (including combination therapy with another immunosuppressive therapy) should be carefully considered and possibly discussed with an oncologist.	IV / C
• Patients should be carefully informed about the increased relative risk of lymphoma in combination therapies involving biologicals with other immunosuppressive agents (particularly thiopurines).	I-II / A
Heart failure	
• In moderate to severe heart failure (ejection fraction ≤ 0.35), anti-TNF-alpha treatment should not be initiated.	I / A

Table 4

Checklist for screening, prophylaxis and critical information prior to initiating anti-TNF-alpha treatment

Name of drug: _____

Prescribing physician: _____

Screening performed by: _____

Indications:

- ❑ Crohn's disease with fistula(s)
- ❑ Crohn's disease without fistula
- ❑ Crohn's disease and extraintestinal manifestations
- ❑ Ulcerative colitis
- ❑ Other

The patient is informed of the treatment and the associated risks	yes	no	
Patient information leaflet distributed	yes	no	
Treatment card distributed	yes	no	
Signs of infection	yes	no	
Tuberculosis (TB)			
IGRA-test (or TST, eventually) performed	yes	no	
Chest X-ray performed	yes	no	
Risk of active or latent TB	yes	no	
Human papilloma virus (HPV)			
Pap smear recommended	yes	no	not relevant
HPV vaccination recommended	yes	no	not relevant
Hepatitis B			
HBsAg, anti-HBc and anti-HBs investigated	yes	no	
HBV vaccination recommended	yes	no	not relevant
Varicella-Zoster virus (VZV)			
Former varicella-herpes zoster infection	yes	no	
VZV vaccination recommended	yes	no	not relevant
Human immunodeficiency virus (HIV)			
HIV risk behaviour	yes	no	
HIV test performed	yes	no	not relevant
Faeces for cultivation (for differential diagnostic reasons)			
Pathogenic intestinal bacteria	yes	no	
Clostridium difficile toxins A + B	yes	no	
Vaccinations (other)			
23-valent pneumococcal vaccine recommended	yes	no	
Re-vaccination every 3rd - 5th year recommended	yes	no	not relevant
Yearly influenza vaccination recommended	yes	no	
Vaccinated with a live vaccine in the last 3 months	yes	no	
	If yes, what and when_____		
Malignant disease within 5 years	yes	no	
Signs of heart failure	yes	no	
Previously allergic reaction to anti-TNF-alpha therapy	yes	no	

Example checklist for use before initiating anti-TNF-alpha therapy (in this case for patients with chronic inflammatory bowel disease)