

Administration of infliximab in general practitioners' offices is safe

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Abstract Infliximab is used in the treatment of various diseases, such as rheumatoid arthritis (RA), psoriasis, psoriatic arthritis (PA), Crohn's disease (CD) and ankylosing spondylitis (AS). In most countries, infliximab is given in hospitals or infusion centers, which are experienced in the management of infusion reactions. Because of this side effect, general practitioners (GPs) might refuse to administer infliximab in their offices. The aim of this study was to investigate the safety of infliximab administration in GPs' offices. Health system in the provincial state of Upper Austria (Austria) provides reimbursement of biological treatment only in outpatient care. Infliximab is due to cost effectiveness usually administered by GPs after a specific training and initialisation of treatment by specialists in the hospital. We sent out a form to 42 cooperating GPs, containing 20 questions concerning the administration of infliximab. Thirty-four forms were returned and evaluated. Altogether, 69 patients (2 patients per doctor mean) were treated with infliximab (1–42 months; 21 months mean). The overall observation period was 697 patients-months. During this period, 487 infusions (14.5 infusions per doctor mean) were administered. From five doctors, seven adverse

events (AE) in six patients were reported. In all seven cases, infusion was discontinued; two had allergic reactions and five had nausea or cardiac symptoms, not definitely of allergic origin. Severe adverse events (SAE), defined as shock, emergency treatment or hospitalisation during or after infliximab administration were reported by two doctors. In contrast, SAE during the infusion of other drugs (e.g. analgetics, vitamins) were previously seen by 16 doctors, showing the overall possibility of infusion reactions with commonly prescribed drugs. Almost all (31/34) confirmed the overall safety of infliximab administration in GP's patient care. The administration of infliximab by specially trained general practitioners with background guidance through rheumatologist or gastroenterologist centers seems to be a safe and acceptable way to provide long-term treatment with infliximab to patients in need of biological treatment.

Keywords General practitioner · Infliximab · Infusion reactions · Rheumatoid arthritis

Introduction

Although the triggering factors for many auto-immune diseases are not known, one of the key inflammatory mediators of the chronic inflammatory process is the pro-inflammatory cytokine tumour necrosis factor- α (TNF- α) [1]. TNF- α overexpression acts as a driver for inflammation that damages the cartilage, bone and bowel mucosa, whereas TNF- α inhibition leads to significant clinical improvements and a reduction of this damage. Infliximab (Centocor, Malvern, PA, USA) is a recombinant human–murine chimeric monoclonal antibody that specifically and potently binds to and neutralises TNF- α [2].

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The implementation of infliximab in the treatment of diseases, such as rheumatoid arthritis (RA) [3], psoriasis [4], psoriatic arthritis (PA) [5], Crohn's disease (CD) [6] and ankylosing spondylitis (AS) [7] dramatically improved symptoms in patients and yielded improved therapeutical options for physicians who are involved in the treatment of these diseases.

TNF inhibitors are generally well-tolerated with prompt onset of action and much earlier relief of symptoms compared with standard disease modifying anti-rheumatic drugs (DMARD) in inflammatory rheumatic diseases or with standard immunosuppressive therapy in Crohn's disease.

Toxicity in the long-term includes serious infections (including a variety of opportunist infections such as pneumocystis and tuberculosis) [8], demyelinating disorders [9] and probably the development of lymphomas; this, however, is still a matter of discussion [10, 11]. In the short-term, major concerns may arise because of possible infusion reactions. Physicians who are not used to the treatment with infliximab may therefore refuse to administer the drug. So it seems reasonable to adequately inform and train health professionals who are involved in the treatment of patients with infliximab.

Austria, though a small country, has, due to its status as a federal republic, nine federal states. In each of these states, the health system, especially the refunding of medical treatment, is handled differently. In Upper Austria, costs of infliximab treatment will not be refunded to hospitals and outpatient clinics. To provide this rather novel and very effective therapy to all patients who are in need of long-term biological treatment, we started a program to include general practitioners (GP) in this specialised treatment strategy. We initiated infliximab therapy in various indications (RA, AS, CD) during a short hospital stay: Patients and their GPs were then informed about all aspects of treatment (indication, administration, pitfalls like allergies and infections).

There are a number of studies, which analyse the safety of infliximab with regard to infusion reactions in the setting of controlled trials or which report the experiences of large infusion centers. However, data on the experience of GPs who administer infliximab in their offices, is sparse. The aim of the present study was to analyse the experiences of our cooperating GPs with the administration of infliximab and to evaluate whether this treatment in GPs' offices is safe.

Materials and methods

After the decision was made to start with infliximab in various indications, the patients were admitted to the hospital for an overnight stay for the first 2 infusions,

which were given 2 weeks apart. All RA-patients received infliximab intravenously in a dosage of 3 mg/kg body weight. All of these patients also received concomitant treatment with methotrexate. In all other indications, infliximab was given in a dosage of 5 mg/kg body weight. The third infusion in week 6 and all succeeding infusions were administered in the GPs offices. After the third infusion, the succeeding dosages were usually given in 8 week intervals. Steroids or antihistamines were not administered routinely for prophylaxes against infusion reactions.

Before starting the treatment with infliximab therapy, GPs were specially trained in all aspects of administration, monitoring and emergency treatment and were able to refuse application, if concerns arose. Specialists prescribed dosage and infusion intervals during patients' routine visits in the rheumatological or gastroenterological outpatient clinic every 3 months.

Evaluation forms containing 20 questions concerning the administration of infliximab were sent to 42 GPs who were all known to administer infliximab for different indications in the area of Linz, the capital of Upper Austria. Thirty-four forms were filled in and returned anonymously (return rate 85%) and evaluated. The indication for the use of infliximab was RA in 33 patients, AS in 19 patients and Crohn's disease in 6 patients.

Results

Altogether, 69 patients (2 patients per doctor mean) were treated with infliximab between 1 and 42 months (21 months mean). The overall observation period was 697 patients-months of treatment. During this period, 487 infusions (14.5 infusions per doctor mean) were administered.

From five doctors, seven adverse events (AE) in six patients were reported. In all seven cases, infusion was discontinued. Two patients had allergic reactions and five had nausea or cardiac symptoms, not definitely of allergic origin. Severe adverse events (SAE) defined as shock, emergency treatment or hospitalisation during or after infliximab administration were reported by two doctors. In contrast, SAE during the infusion of other drugs (e.g. analgetics, vitamins) were previously seen by 16 doctors, showing the overall possibility of infusion reactions with commonly prescribed drugs. All but two doctors rated themselves as experienced in shock management. Most of the GPs (27/34) would decide about the continuation of the infliximab therapy in case of an AE together with the background rheumatologist (gastroenterologist) and 21/34 routinely report any AE to the Ministry of Health. Almost all (31/34) confirmed the overall safety of infliximab administration in GP's patient care. Only 7/34 would

prefer treatment in outpatient clinics. The overall confidence with the actual regime was estimated as very good by 19, mostly good by 7, sufficient by 4 and not good by 2 (2 no answers).

Discussion

Infliximab is a biologic response modifier, which significantly improves symptoms and signs, function and quality of life in patients with chronic inflammatory and rheumatic conditions. It induces and maintains remission and reduces objectively measured damage.

To reduce the concerns about AEs, GPs we are cooperating with were trained in the handling of infliximab. Typically, infusion reactions were present within 1–2 h. For instance, in the ACCENT I trial [6], which tested the efficacy of infliximab in CD, infusion reactions were noted in 5% of the infliximab arm and in 3% of the placebo arm. Symptoms included headache, vertigo, nausea, flush, fever, chills, cough, dyspnoea and thoracic pain. Lequerre et al. who analysed infusion reactions in patients with RA or AS, found an overall rate of acute reactions of 11.3% [12]. However, whether infusion reactions are typically a type I hypersensitivity reaction is a matter of debate. It is argued that IgE-mediated reactions compose the minority of infusion reactions because they commonly disappear with reduced speed of infusion. They are often noted within the first infusion and several of them develop after the first hour of infusion, while serum tryptase levels—a marker of mast cell activation—are usually within the normal range [13]. However, there is evidence that antibodies directed against infliximab (HACA) are involved in the development of infusion reactions. The presence of this anti-chimeric antibody production is related to the murine sequences in the molecule. The likelihood that biotechnologically manufactured drugs will produce a host immune response is dependent on the quantity of ‘foreign’ material. Infliximab contains 75% human protein and 25% murine protein. Higher titers of antibodies against infliximab are associated with an increased risk of infusion reactions and also with a reduced efficacy of treatment. Concomitant immunosuppressive therapy seems to reduce the titers of antibodies against infliximab and the number of infusion reactions [14]. In addition, the frequency of antibody production was found to be inversely related to the amount of infliximab infused. This phenomenon is assumed to represent high zone tolerance.

In general, infusion reactions after the administration of infliximab are not seldom, but are usually mild to moderate. They are similar to infusion reactions observed during intravenous administration of other drugs. Anaphylactic reactions are infrequent, but can result in the

discontinuation of the treatment. In the case of mild reactions, the infusion should be temporarily stopped and the patient should receive saline infusions, antihistamines and corticosteroids intravenously. When the symptoms have resolved, the infusion can be re-started with caution at a slower rate. Most patients respond adequately to the treatment and can complete the infusion. Patients with severe reactions should receive higher doses of antihistamines and corticosteroids. Depending on the situation, epinephrine may be considered. The administration of infliximab in such cases should be definitely stopped. However, in single cases, continuation at a very slow infusion rate can be considered under careful monitoring of the patient. Patients who have already shown an infusion reaction may benefit from antihistamines and corticosteroids given intravenously 30 min before the infusion of infliximab.

Conclusion

The administration of infliximab by specially trained general practitioners with background guidance through rheumatologist or gastroenterologist centers appears to be a safe and acceptable way to provide long-term treatment with infliximab to RA, AS and Crohn’s patients in need of biological treatment.

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