Immediate Infusional Reactions to Imunobiological Drugs: Experience of Procedures in an Infusional Center

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Abstract
Recently, many drugs are used in Dermatology, Rheumatology and Gastroenterology and many are the routes of application. The aim of this article is to analyse the immediate infusional reactions that happen during or in the 30 minutes following the infusional procedure. Abatacept, Adalimumab, Etanercept and Ustekinumab were the immunobiological drugs used in a Infusional Center, located in Belo Horizonte, Minas Gerais, during one year, for the treatment of dermatological, rheumatological and gastroenterological diseases. A retrospective study has been done and the informations were withdrew from patients’ files. Secrecy was maintained as only names’ initials were used.

Keywords: Immediate infusional reactions; Infusional center; Immunobiological drugs; Immunomediated diseases

Introduction
Nowadays, several are the immunobiological drugs and many are the application routes. So, in dermatology, we have Ustequinumab [1] Infliximab [2] Etanercept [3], and Adalimumab [4,5] all of them approved of by FDA for treatment of psoriasis and arthritis. In rheumatology, immunobiologics are used in the treatment of reumathoid arthritis [6], juvenil arthritis, ankylosing spondylitis [7], lupus [8]. Immunobiologics are also used in Gastroenterology [9].

Immunobiological drugs era used in the treatment of diseases like psoriasis, psoriatic arthritis, reumathoid arthritis, ankylosing spondylitis, lupus, Crohn’s disease, ulcerative retocolitis. Their route of application can be endovenous or subcutaneous. At the beginning, infusions were done in oncologic clinics and side effects related to the drugs were described in oncologic papers [10]. But patients using immunobiologics are more predisponed to infections [11]. And the oncologic patients, because of the medicines they use, have a higher risk of contracting infections, which can be disseminated to patients in use of immunobiological drugs. Furthermore, patients with benign diseases and sometimes emotionally shaken, have a fear of having the same side effects of oncologic treatments, as hair loss [12], that can be seen in the patient besides them. That was the beginning of the Infusional Centers for the use of immunobiological drugs in immunomediated diseases.

Methods
A previous study demonstrated the side effects that had happened during or 30 minutes after the endovenous application of some immunobiologics, in a Infusional Center in Brazil [13]. The aim of this article was to demonstrate, during a period of one year, the side effects we could see in a Infusional Center, located in Belo Horizonte, during endovenous or subcutaneous application of immunobiological drugs.

From November 2014 to March 2016, data were collected from patient’s filles, preserving their privacy. Only the name’s initial letters were used. Patients who received Infliximab (Endovenous route) Abatacept (by endovenous route), Etanercept (subcutaneous route), Adalimumab (subcutaneous route) were questionned about side effects during or 30 minutes after receiving these immunobiological drugs.

The drug used, estimated dose and indication were determined by the patient’s doctor. Temperature, blood pressure and heart frequency were measured in all patients, following the clinic’s protocol.

The patients were questionned about signs of infection, what contra indicated the infusion.

i. Infliximab was applied via endovenous, 24 dpm (drops per minute)
Abatacept was applied endovenous, 40 drops per minute

Etanercept and Adalimumab were applied subcutaneous

All the patients who were submitted to an endovenous route of application received pre-infusional medication, like Acetaminofen and anti histamine drugs before infusion; patients answered a questionnaire in which doctors could detect any kind of infection or other signs or symptoms which contra indicated infusion. Temperature, blood pressure and heart frequency were monitored each 15 minutes, by the nurse or by the doctor. The patient was also questioned about side effects during or 30 minutes later the infusion. For standardization, we grouped the side effects according to systems. The adopted classification was the following: angioedema, cutaneous, gastrointestinal, hemodynamic, musculoskeletal, neurologic, respiratory or mixed (when there was multissystemic envolvement).

The classification concerning the severity of the reaction was based in the Common Terminology Criteria for Adverse Events [14].

A. **Mild reaction:** Mild and transitory reaction, when the interruption is not indicated

B. **Mild moderate reaction:** when the interruption is indicated, but with immediate response to a symptomatic treatment

C. **Moderate reaction:** Immediate response to symptomatic medication, recurrence after initial response, hospitalization is indicated

D. **Serious reaction:** Risk of death

E. **Very serious reaction:** Death

**Results**

Infusions: 412

A. Immunobiological Drugs
   i. Infliximab 89 infusions
   ii. Etanercept 149 infusions
   iii. Abatacept 72 infusions
   iv. Adalimumab 72 infusions

B. Side Effects

**Infliximab**

i. Angioedema not detected

ii. Cutaneous not detected

iii. Gastrointestinal not detected

Hemodynamic 21

i. Musculoskeletal not detected

ii. Neurological not detected

iii. Respiratory not detected

iv. mixed not detected

C. **Etanercept**

i. Angioedema not detected

ii. Cutaneous 2 ( bruise)

iii. Gastrointestinal not detected

iv. Hemodynamic 1 ( Bradycardia)

v. Musculoskeletal not detected

vi. Neurological not detected

vii. Respiratory not detected

viii. mixed not detected

a. **Adalimumabe**

i. Angioedema not detected

ii. Cutaneous not detected

iii. Gastrointestinal 1 Diarrhea

iv. Hemodynamic not detected

v. Musculoskeletal not detected

vi. Neurological not detected

vii. Respiratory not detected

viii. mixed not detected

b. **Abatacepte**

i. Angioedema not detected

ii. Cutaneous not detected

iii. Gastrointestinal not detected

iv. Hemodynamic 11 (higher blood pressure during the infusion)

v. Musculoskeletal not detected

vi. Neurological not detected

vii. Respiratory not detected

viii. mixed not detected

**Discussion**

Infliximab is a monoclonal antibody (anti TNF alfa) [15]. According to the literature the majority of side effects related to the drug was mild to moderate and included: dyspnoea, urticaria and headache.
Etanercept is a humanized fusion protein. It is a TNF transmembrane competitive blocker. According to the literature, the most common side affected is a reaction in the site of injection. Adalimumab is a human monoclonal antibody. The side effect more frequently seen is the reaction in the site of injection. Increased infections, mainly airways infections and genitourinary infections. Rare cases of anaphylaxis have been reported, as well as thrombocytopenia. Adalimumab may induce FAN and anti DNA formation and Lupus like syndrome.

Abatacept is a fusion protein CTLA-4-IgG that acts like inhibitor molecules co stimulating T lymphocytes. Abatacept is indicated for patients with Rheumatoid Arthritis who had failed to DMARDS or anti TNF agents. It can be used isolated or associated to anti TNF. Abatacept is to be administered as an endovenous infusion over 30 minutes at a dose of 500mg in patients less than 60kg, 750mg in patients between 60-100kg and 1000mg in those with more than 100kg body weight. The next dose should be administered two and four weeks after the initial dose and then every four weeks. The use of abatacept is associated with a higher incidence of infectious complications when compared to placebo, as observed with other biological DMARDs.

The infusion reactions with abatacept are uncommon and are mainly Hypersensitivity reactions manifested by rash or bronchospasm. It is contraindicated in patients with chronic obstructive pulmonary disease frame (COPD) due to exacerbation of dyspnoea and increased occurrence of infections [16].

According to the literature, the most common infusion reactions are: erythema, urticaria, eczema or a rash which may, in turn, be accompanied by pain or edema. 3 headache, nausea, dizziness. According to our observation, the most common infusional reactions were: higher of blood pressure, during the infusion, temporary bruise in the site of injection, hypotermia, diarrhea, bradycardy. The incidence of site effects observed in our clinic was around 38 within 412 related cases. That corresponds to less than 10 percent of the total number of infusions. Concerning to gravity of the reactions, the majority of patients showed mild reactions.

Many doctors seem to fear the immunobiological drugs and their side effects. But, regarding to pre infusional anamnesis, low rate of infusion and follow up of the patient during the whole infusion, these drugs seem to be safe and with a low rate of side effects.

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