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Original article

Immediate infusional reactions to intravenous immunobiological agents for the treatment of autoimmune diseases: experience of 2126 procedures in a non-oncologic infusion centre

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ABSTRACT

Introduction: With the increasing use of immunobiological drugs (IBD), the knowledge about their effectiveness and safety has increased.
Objective: To analyze the immediate infusional reactions (IIR) to intravenous IBD: infliximab (IFX), rituximab (RTX), abatacept (ABT) and tocilizumab (TCZ) on the treatment of autoimmune diseases.
Method: 2126 infusions performed in the Infusion Centre - CID in 268 patients were analyzed. The used drug, its clinical indication, infusion time, and use of premedication were determined by the prescribing physician. All intercurrences presented during infusion and/or during a thirty minutes observation period were considered as IIR. The approach adopted in IIR followed the protocols of the Infusion Centre - CID.
Results: Regarding the type of IBD, the infused drugs given were: IFX (1584, 74.5%), TCZ (226, 10.63%), RTX (185, 8.7%) and ABT (131, 6,16%). IIR were described in 87 procedures (9.4%): 77 - IFX group and 10 - RTX group. IIR were not described in ABT and TCZ groups. Most were considered as mild (n = 5; 41.17%) or moderate (n = 50, 58.81%) reactions; there were no serious reactions. Regarding to discontinue infusions, 79 (92.9%) were resumed and completed successfully. Only six (0.28% of infusions) were not completed because of IIR.
Conclusion: Despite the differences between the number of procedures per drug, ours is a "real life" analysis, where the incidence of IIR was similar to that described in the literature. The low incidence of IIR corroborates the safety data, both quantitatively and qualitatively, and underscores the importance of specialized medical support during infusion.

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Reações infusionais imediatas a agentes imunobiológicos endovenosos no tratamento de doenças autoimunes: experiência de 2.126 procedimentos em um centro de infusão não oncológico

Palavras-chave:
Reações infusionais imediatas
Imunobiológicos
Doenças autoimunes

RESUMO

Introdução: Com o crescimento do uso de drogas imunobiológicas (IBD) ampliamos o conhecimento sobre sua eficácia e segurança.
Objetivo: Analisar as reações infusionais imediatas (RII) às IBD endovenosas – infliximabe (IFX), rituximabe (RTX), abatacepte (ABT) e tocilizumabe (TCZ) – no tratamento de doenças autoimunes.
Método: Avaliamos 2.126 infusões feitas no CID (Centro de Infusão) em 268 pacientes. A droga usada, a indicação clínica, o tempo de infusão e o uso de pré-medicação foram determinados pelo médico prescritor. Foram consideradas RII todas as intercorrências apresentadas durante a infusão e/ou período observacional de 30 minutos. A conduta adotada nas RII seguiu os protocolos do CID.
Resultados: Em relação ao tipo de IBD, as infusões foram distribuídas em: IFX (1.584; 74,5%), TCZ (226; 10,63%), RTX (185; 8,7%) e ABT (131; 6,16%). As RII foram descritas em 87 procedimentos (4,09%): 77 no grupo IFX e 10 no grupo RTX. Não foram descritas RII nos grupos de ABT e TCZ. A maioria foi considerada leve (n = 5; 41,17%) ou moderada (n = 50; 58,81%) e não houve reações graves. Das infusões interrompidas, 79 (92,9%) foram reiniciadas e concluídas com êxito. Apenas seis (0,28%) não foram concluídas por causa das RII.
Conclusão: Apesar da diferença entre o número de procedimentos por droga, trata-se de uma análise de "vida real", na qual a incidência de RII foi semelhante à descrita na literatura. A baixa incidência de RII corrobora os dados de segurança tanto de forma quantitativa como qualitativa e ressalta a importância do acompanhamento médico especializado durante a infusão.

Introduction and objectives

With the growing use of immunobiological drugs (IBD) in the treatment of various autoimmune diseases, it has been possible to increase our knowledge about their effectiveness and safety.

Currently several substances with different mechanisms of action and routes of administration are available, and their use is becoming increasingly common in specialties such as Rheumatology, Dermatology and Gastroenterology.[1]

Much of the knowledge about immediate infusional reactions (IIR) of intravenous (IV) IBD is based on results of phase II and III clinical studies, or on experiences during oncology treatment protocols.[2,3] It is therefore necessary to deepen these studies in patients with autoimmune diseases, as well as to apply them in groups of patients in everyday clinical practice;. the "real life". This study aimed to describe the prevalence, severity and outcomes of IIR from the use of IV IBD in a Non-Oncology Infusion Centre (CID) – a "real life" scenario of the application of these drugs in the treatment of different autoimmune diseases.

Materials e methods

Sample

A total of 2126 infusions of IBD IV: infliximab (IFX), tocilizumab (TCZ), rituximab (RTX) and abatacept (ABT), were performed in a total of 268 patients undergoing treatment for autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease, psoriasis, systemic lupus erythematosus, Sjogren's syndrome, systemic vasculitis, uveitis, dermatomyositis, pemphigus and antiphospholipid antibody syndrome), were evaluated. These infusions were held on the premises of the Infusion Centre - CID, from October 2006 to November 2011.

The administered drug and its dose, clinical indication, infusion time (provided the adherence to the minimum infusional time of each drug given in the package insert: IFX,[4] 2 hours; TCZ,[5] 1 hour; RTX,[6] 4 hours; ABT,[7] 30 m) and with or without premedication were determined by the attending physician, according to prescriptions and medical reports, except for the RTX group, in which pre-infusional medication was used in all procedures, which necessarily included corticosteroids and anti-histamines PO or IV. The premedication used during IFX, TCZ and ABT infusions varied according to the prescription of the attending physician, but in all cases consisted of corticosteroids IV and/or anti-histamines PO or IV.

Regarding the dose of IV IBD, only in RTX group a standard dose of 1 g/infusion was used. For the other drugs, the dosage established by the prescribing physician was kept. The different doses used in groups IFX, TCZ and ABT, as well as the drip type used for drug infusion are detailed in Table 1. An infusion pump was only used in RTX infusions.

All infusions were performed intravenously and preceded by medical evaluation. Vital signs measurements were performed during and at the end of infusional period.

No data on the use of concomitant drugs, disease activity indexes or treatment failure were collected.

Immediate reactions

For the present study, IIR were considered as the intercurrences, symptomatic or not, present during the infusion and/or subsequent observational period of 30 minutes. These IIR were classified according to the type of event, severity and time of event after the start of infusion (Table 2). To facilitate the reaction classification, these were grouped according to systems, adopting the following division: angioedematous, cutaneous, gastrointestinal, hemodynamic, musculoskeletal, neurological, respiratory or mixed (when there was multisystemic involvement). To assess the severity of IIR, the National Cancer Institute event severity scale[8] was used (Table 2). The approach adopted in IIR followed the protocols for intercurrences of the Infusion Centre - CID, dividing cases regarding the use or lack of rescue medication, with or without temporary interruption of the infusion and/or cessation of infusion (Table 2).

Statistical analysis

Data was stored using a Microsoft Access 2007 database and analyzed with Prism 4.0 software. The results were presented in absolute percentage (%), considering the total number of infusions; and relative percentage (%), considering the subgroups analyzed (type of drug and IIR). Due to the retrospective nature of the analysis, informed consents were not obtained, but patients' data were protected by numeric codes.

Table 1 – Distribution of IIR by drug × number of drug infusions and elapsed infusion time.

	Infliximab 1584 Reactions = 77 n (%)	Rituximab 185 Reactions = 10 n (%)	Total 2126 87 n (%)
Number of infusions			
1st	13 (16.88)	6 (60)	19 (21.83)
2nd to 4th	23 (29.87)	4 (40)	27 (31.03)
5th to 8th	18 (23.37)	-	18 (9.19)
9th to 16th	16 (20.77)	-	16 (18.39)
After 16th	7 (9.09)	-	7 (8.04)
Infusion Time			
< 30 min.	21 (27.27)	-	21 (26.25)
30-60 min.	26 (33.76)	2 (20)	28 (35)
60-120 min.	16 (20.77)	3 (30	19 (22.5)
> 120 min.	5 (6.49)	1 (10)	6 (6.25)
NI	9 (11.68)	4 (40)	13 (17.56)
Outcome			
Resumed after initial measures, and finalized	69 (89.61)	10	79 (90.8)
Suspension of procedure after initial measures	4 (5.19)	0	4 (4.59)
New IIR after initial steps - successful completion	2 (2.59)	0	2 (2.29)
New IIR after initial steps - suspension of procedure	2 (2.59)	0	2 (2.29)

Results

IBD infusions

During the period between October 2006 and November 2011, a total number of 268 patients with autoimmune diseases were treated with IV IBD at the Infusion Centre, totalling 2126 infusions performed. Regarding the type of drug used, the infusions were distributed as follows, in order of prevalence: IFX, n = 1584 (74.50%); TCZ, n = 226 (10.63%); RTX,

Table 2 – Classification of the severity of IIR according to NCI and Infusion Centre - CID protocol of intercurrences. Adapted from Common Adverse Events Terminology Criteria v4.02 (CTCAE).[8]

Severity of IIR		Infusion Centre - CID - Intercurrence Protocol
Grade	Description	Procedure adopted at the Infusion Centre - CID
1 - mild	Mild and transient response, no indication of interruption of the infusion; no indication of intervention	No need for intervention.
2 – mild/ moderate	Indication for therapy or discontinuation of the infusion, but with no immediate response to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids), Prophylactic medications indicated for ≤ 24 hours	Temporary interruption of the infusion, use of rescue medication, if necessary; infusion resumed after complete resolution of symptoms.
3 – moderate	Brief or prolonged interruption of the infusion (e.g., no rapid response to symptomatic medications); recurrence of symptoms after initial improvement: hospitalization indicated for other clinical sequelae	Temporary interruption of the infusion and use of rescue medication; infusion resumed after complete resolution of symptoms. Consider discontinuation of the procedure.
4 – severe	Life-threatening consequences; urgent intervention indicated	Interruption of the infusion and use of rescue medication and hemodynamic support. Discontinuation of the procedure.
5 – severe	Death	Death

n = 185 (8.7%); and ABT, n = 131 (6.16%) (Fig. 1). The distribution of patients by drug and means of infusions performed in each group are presented as follows: IFX = 168 (62.68%) patients with a mean of 9.42 infusions/patient (1-32); RTX = 59 (22.01%) patients with a mean of 3.13 infusions/patient (1-12); TCZ = 26 (9.70%) patients with a mean of 8.60 infusions/patient (1-23); and ABT = 15 (5.59%) patients with a mean of 8.70 infusions/patient (1-39).

It is important to note that, considering the characteristics of the study, a single patient may have been subjected to more than one type of treatment. Regarding the distribution of the registered diagnosis, the most frequent diagnosis was rheumatoid arthritis, n = 805 (37.86%), followed by inflammatory bowel disease, n = 416 (19.56%), ankylosing spondylitis, n = 376 (17.68%), psoriasis, n = 237 (11,14%), psoriatic arthritis, n = 185 (8.7%), and others (systemic lupus erythematosus, Sjogren's syndrome, systemic vasculitis, uveitis, dermatomyositis, pemphigus and antiphospholipid antibody syndrome), n = 107 (5.03%). All RTX infusions were preceded by pre-medication, also used in 530 IFX infusions (33.45%), 1 TCZ infusion (0.44%) and 1 ABT infusion (0.76%). As to the dose used, 925 IFX infusions (58.39%) doses applied were between 3 and 5 mg/kg, 582 infusions (36.74%) with doses > 5 mg/kg and 77 infusions (4.86%) with doses < 3 mg/kg. In TCZ group, doses ≤ 8 mg/kg were used in 143 procedures (63.27%); in 83 infusions (36.72%) doses > 8 mg/kg were used. For the ABT group, the most widely used dose was 750 mg/infusion, totalling 99 infusions (75.57%), followed by 500 mg, with 22 infusions (16.79%) and 250 mg, with 10 infusions (7.63%).

Immediate infusion reactions (IIR)

Of 2126 infusions, IIR were documented in 87 procedures (4.09% of total infusions), with 77 events in the IFX group (88.50% of total reactions and 4.86% of IFX infusions) and 10 in the RTX group (11.49% of total reactions and 5.40% of RTX infusions). In groups ABT and TCZ, IIR were not described (Fig. 1, Table 3).

Regarding severity, IIR classified as moderate were the most frequent, reported in 50 (57.47%) infusions; followed by mild IIR, occurring in 37 procedures (42.52%) (Table 3). No serious reaction was reported.

In terms of clinical presentation, the most common reactions were purely cutaneous (rash, itching, redness, urticariform lesions), described in 21 IIR (24.13%) cases, followed by 19 mixed (multisystemic) (21.83%), 17 hemodynamic (tachycardia, changes in blood pressure) (19.54%), 9 angioedematous (10.34%), 7 gastrointestinal (nausea, vomiting, abdominal pain) (8.04%), 5 respiratory (bronchospasm, dyspnea, coughing) (5.74%), 5 musculoskeletal (low back pain, arthralgia, myalgia) (5.74%), and 3 neurological (headache, drowsiness, confusion) (3.44%) reactions (Table 3). In the present study, the relation between IIR and underlying disease was not addressed.

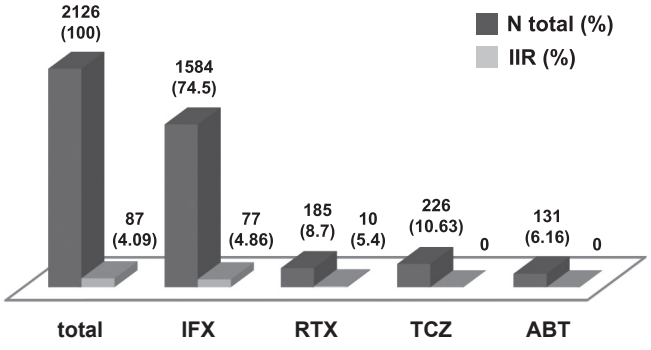

Fig. 1 – Total and percentage of infusions and IIR by drug.

Regarding post-IIR outcomes in 60 cases of IIR (68.96% of total IIR), the drip was discontinued as an initial measure, and in 72 cases (82.75%) the use of rescue medication (antihistamines, corticosteroids, analgesics, adrenaline) was required (Table 3). Of the IFX related IIR, 36 (46.75%) occurred until the fourth infusion, and 54 (70.12%) until the eighth; in the majority of the cases, 47 (61.03%), IIR occurred within the first hour of the procedure (Table 1). Regarding infusions of RTX, the 10 IIR cases reported occurred until the fourth infusion of the drug, and eight (80%) were reported at the first infusion of the application cycle (D0) and 2 (20%) during the second infusion (D15). Importantly, the two cases of IIR in D15 occurred in patients who had already suffered IIR in D0.

Regarding the dose used, most of the IFX related IIR occurred at doses of 3 mg/kg and 5 mg/kg (50 - 64.93%), followed by doses > 5 mg/kg (26 - 33.76%) and < 3 mg/kg (1 - 1.29%).

In the present study, the use of premedication was determined by the prescribing physician. The preparation was

Table 3 – Classification of IIR by drug, severity, clinical presentation and behaviour.

	Infliximab 1584 n (%)	Rituximab 185 n (%)	Total 2126 n (%)
Immediate infusional reaction (IIR)			
Yes	77 (4.86)	10 (5.40)	87 (4.09)
No	1507 (95.14)	175 (95.60)	2039 (95.91)
Severity			
Mild	33 (42.87)	4 (40)	37 (42.52)
Moderate	44 (57.13)	6 (60)	50 (57.47)
Severe	-	-	-
Reaction type			
Angioedema	6 (7.79)	3 (30)	9 (10.34)
Purely cutaneous	19 (24.67)	2 (20)	21 (24.13)
Purely gastrointestinal	5 (6.49)	2 (20)	7 (8.04)
Purely neurological	1 (1.29)	2 (20)	3 (3.44)
Purely musculoskeletal	4 (5.19)	1 (10)	5 (5.74)
Purely respiratory	5 (6.4)	-	5 (5.74)
Purely hemodynamic	17 (22.07)	-	17 (19.54)
Multisystemic	19 (24.67)	-	19 (21.83)
Other	1 (1.29)	-	1 (1.14)
Infusion interruption			
Yes	56 (72.72)	4 (40)	60 (68.96)
No	21 (27.27)	6 (60)	27 (31.03)
Rescue medication[a]			
Yes	65 (84.41)	7 (70)	72 (82.75)
No	12 (15.58)	3 (30)	15 (17.24)

[a] Antihistamines, corticosteroids, analgesics, adrenaline.

prescribed in 33.72% of infusions, and in 52.87% of IIR cases, patients were pre-medicated. Of the six procedures in which the infusion could not be completed due to IIR, 3 (50%) were preceded by premedication.

Of all IIR observed, 79 (90.8%) cases were solved using initial manoeuvres (interruption of the infusion and/or use of rescue medication) and the procedure was successfully concluded, with no further intercurrences. In two IFX infusions, there was no recurrence of reactive symptoms after initial measures, even after required further intervention, which resulted in a successful procedure. In 6 infusions, all from the IFX group (7.79% of IIR cases with IFX use and 0.37% of total IFX infusion), it was not possible to complete the procedure due to the severity or non-resolution of the reactive picture, and the infusion was discontinued. All IIR related to RTX were reversed and the procedure was completed successfully. As an overall result, of the 2126 procedures, only 6 (0.28%) were not completed due to IIR.

Discussion

General reactions

Essentially, the infusional reactions are classified in allergic (IgE-mediated or of hypersensitivity type I) and non-allergic (non-IgE, generally attributed to cytokine release) reactions.[9,10] The majority of infusional reactions related to the infusion of monoclonal antibodies pertain to the non-allergic type,[11] but in practice, as the symptoms are very similar, it is difficult to classify clearly the nature of the reaction, especially for autoimmune diseases, which exhibit differentiated pathophysiological patterns in relation to neoplastic diseases.[3] In practice, we found that the reactions mediated by the release of cytokines, in contrast to those that are mediated by IgE, usually resolved with temporary drip suspension and by administration of antihistamines; these procedures allowed to return to infusion.

Acute reactions to the infusions of monoclonal antibodies are described mostly as mild to moderate [levels 1 and 2, according to the classification published by the National Cancer Institute (Table 2)], and the incidence of severe reactions is small.[11-14] In studies using monoclonal antibodies to treat cancer, the reactions are described as more frequent during the first infusions, and generally managed successfully after a temporary reduction or cessation of infusion and the use of an appropriate rescue medication. Most patients tolerate well the subsequent infusions with the use of premedication.[6,15,16] The results of this study are in line with literature data, since most of the observed reactions allowed resuming the infusion after initial measures and occurred more often in the initial procedures.

One added obstacle in the analysis of comparative studies is the lack of standardization of nomenclature and of the reaction classification of the series, since the designation "infusional reaction" can be found as "allergic reaction", "acute infusional reaction", "immediate infusional reaction" and other terms, generating a possible bias in the interpretation of results. In our analysis, considering that all intercurrences were classified as IIR, without distinction as to whether or not allergic in nature, the results should be interpreted considering this broader and less specific concept. It is also necessary to emphasize that the overall percentages of IIR observed in our study may also have been influenced by the pre-medical consultation conducted by medical staff of the Infusion Centre - CID before every infusion, with the main goal of an early detection of absolute contraindications prior to the infusion.

Infliximab

IFX is a chimeric (murine-human) monoclonal antibody that binds to TNF (tumour necrosis factor), used successfully for the control of several autoimmune diseases.[1] Among the IV IBD evaluated in this study, IFX is the one that has most indications in the package insert (i.e., rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease and psoriasis). Since the recommended dosages are different for each disease indicated (from 3 to 10 mg/kg/infusion),[4] it was necessary to divide the analyzed procedures by dose/kg body weight (Table 1).

In a study that compared percentage of discontinuation of IFX, etanercept and adalimumab (two other IBD acting on TNF, but whose route of administration is subcutaneous), the proportion of discontinuations caused by IIR in IFX users was 23.9%, above the average of the other anti-TNF (16%) and of each drug considered individually.[17] Possibly because IFX is the only anti-TNF agent for IV use available in Brazil, it is the drug most related to IIR occurrence in its group. In the literature, the risk of IIR in IFX users ranges from 0.8% to 8.8% by infusion.[18-24] In most cases, the IIR are considered mild or moderate. Reports describe a frequency of severe reactions around 0.5%, and only 2% of patients discontinued the treatment due to infusional reaction.

In patients with Crohn's disease, the reported frequency of IIR is 4%-5%, half of which occur until the third infusion (25% until the second infusion).[25] These values are closer to those observed in our study (4.86%), which included patients with different pathologies.

We emphasize that from the procedures analyzed at the Infusion Centre - CID, in 21 cases of IIR (27.27%) there was no need to interrupt the drip, and in two cases even after a recurrent reactive manifestation, it was possible to complete the procedure. Only in 6 procedures (7.79% of IIR and 0.37% of all infusions of IFX performed) the infusion was not completed when it became imperative to discontinue the medication.

The symptoms most frequently described in IIR are headache, dizziness, nausea, rash and pruritus.[21,23,24,26] In our study a greater relative proportion of hemodynamic changes (hypo- or hypertension, tachycardia) was noted, being second in frequency only for cutaneous reactions.

Despite the high frequency of reactions described in the literature, and despite some studies that encourage the use of premedication in IFX infusions, most of the studies with an adequate design do not recommend the use of antihistamines or steroids in preparation for infusion in patients naïve to transfusional reactions.[21,27,28] Regarding the use of premedication, in 52.87% of cases of IIR premedication was used suggesting that the use of this strategy did not help avoid the occurrence of IIR. We emphasize that in some premedication cases its use occurred in patients who had previously suffered

of IIR, which determines a bias in data analysis. However, we emphasize the low frequency of IIR among patients not premedicated (5%), which agrees with the literature and suggests that the routine use of premedication is not justified in patients naïve to previous reactions. Likewise, and even in face of the small number of events, the use of the drug preparation apparently did not change the IIR outcome, since there was no difference for this criterion among the suspended procedures due to IIR.

Tocilizumab

TCZ is a recombinant humanized monoclonal antibody that blocks interleukin-6 receptor that plays a fundamental role in the pathophysiology of rheumatoid arthritis. The reported frequency of infusional reactions in the literature is around 7%. The most common symptoms are transient elevation of blood pressure, redness at the site of venipuncture, headache, nausea and rashes.[29,30] Usually, IIR are mild and transient, allowing the treatment maintenance. The absence of IIR related to TCZ in this study should be interpreted with caution, due to the small number of procedures performed, 226, which accounted for only 10.63% of all procedures. We believe that the results obtained in our study favour the infusional safety of TCZ.

Rituximab

RTX is a chimeric (murine-human) anti-CD20 monoclonal antibody originally used for the treatment of non-Hodgkin lymphoma protocols, and is also approved for the treatment of rheumatoid arthritis.[6] In other autoimmune diseases such as systemic lupus erythematosus, dermatomyositis and some systemic vasculitides. RTX has shown efficacy and presents itself as a good off-label therapeutic option. Compared to studies of non-Hodgkin lymphoma and leukemias, diseaser where RTX is commonly used for extended amounts of time, the knowledge about the use of this drug for autoimmune diseases is still limited.[18] Perhaps this is one reason to explain the large discrepancy between data about RTX infusional safety.

As determined in previous studies and recommendations of the manufacturer,[6] infusions of RTX must be preceded by some drug preparation (antihistamines, corticosteroids and acetaminophen). This protocol, developed for the treatment of lymphoma, is also adopted in the care of patients with autoimmune diseases, and has been used in infusions performed at the Infusion Centre - CID.[31,32]

Studies show that the incidence of IIR related to RTX use can be greater than 70%, but there is evidence that this number may vary according to the indicated disease, and the reactions are more frequent in the treatment of neoplasms (12% in systemic vasculitis, 27% in rheumatoid arthritis and 77% in non-Hodgkin lymphoma), for unknown reasons.[33] A study that analyzed the safety of RTX only for autoimmune diseases in 370 patients showed a much lower incidence of IIR (around 18%), and only 2.4% of treatment discontinuations for severe reaction were required. When a secondary analysis was taken, it was found that the risk of reaction per patient did not exceed 2%, and there was no statistically significant difference between the conditions.[35]

Similar to anti-TNF reactions, the RTX reactions are more common during the initial infusions, and occur most frequently within the first two hours of infusion. The proportion of IIR dropped by half from the first to the fourth infusion.[12,34] The most common symptoms reported are urticaria, hypotension, angioedema, hypoxia and bronchospasm, but there are also reports of respiratory failure, myocardial infarction, cardiogenic shock and severe anaphylaxis.[28]

As severity, most IIR are of mild to moderate intensity. The literature describes around 10% of severe reactions, in rare cases leading to death. Certain information of particular interest is that 80% of cases of death related to the infusion of RTX occurred at the first round of infusion of the drug.[34] In our series, the incidence of IIR related to RTX (in 69.72% of cases with indication of rheumatoid arthritis treatment) was much lower (5.40%), however with a similar pattern to that described in the literature. All IIR were considered of mild or moderate intensity (no severe reactions in this series), and occurred until the second infusion, 60% of them during the first procedure. Despite the reactions presented, all 185 infusions of RTX held at the Infusion Centre - CID in the study period were completed successfully. During no procedure the discontinuation of the infusion due to IIR was needed.

Abatacept

ABT is a fusion protein that blocks and modulates a key costimulatory signal, promoting downregulation of T cells.[7] The condition most commonly used for are rheumatoid arthritis[36,37] and juvenile idiopathic arthritis.[38]

The frequency of IIR assigned to ABT use in the literature is about 9%.[39] Specific studies in juvenile idiopathic arthritis show percentages around 4%.[38] A systematic review describes that the rate of discontinuation of ABT because of serious adverse events (including severe anaphylaxis) is significantly lower than that of IFX.[39] A subgroup analysis, however, pointed out that the frequency of adverse events is higher in patients with chronic obstructive pulmonary disease and diabetes mellitus. Considering that it was not the aim of our study to evaluate the relationship of IIR with comorbidities, it was not possible to attribute the absence of IIR to the use of ABT due to patient characteristics; however, it should be emphasized that the existence of obstructive lung disease is a contraindication related to the use of ABT.

Regarding the absence of IIR in the 131 infusions (6.16% of infusions) of ABT in this study, the same comments for the TCZ group and the expectation of equally promising results in relation to the infusional safety profile of this drug are pertinent.

We recognize that the main limitation of the combined data analysis in our study was the discrepancy among the number of IFX infusions, when compared to the other three drugs. Some conditions justify this finding:

1) The time span of these drugs in the Brazilian market for non-oncological use: Infusions performed from October 2006 on were evaluated, when IFX was the only available drug in Brazil. The first infusion of the other drugs at the Infusion Centre - CID occurred in September 2007 (ABT), October 2007 (RTX) and September 2009 (TCZ).

2) Number of indications in the package insert: IFX has five indications: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis and psoriasis, while other drugs have only one indication: rheumatoid arthritis.
3) Posologic schedule (frequency of infusion): IFX: infusions every 6-8 weeks, with plus 3 infusions/year in the case of induction therapy; RTX: maximum of 4 infusions/year (2 infusions, twice a year); TCZ: infusions every 4 weeks; and ABT: infusions every 4 weeks, plus one infusion/year in case of induction therapy.

Thus, the presented results cannot be interpreted in a comparative manner between different drugs, but are significantly useful to reflect the practical treatment routine of autoimmune diseases with IV IBD.

Conclusions

Despite a heterogeneous distribution of the number of procedures for these drugs, we believe that the results reflect the analysis of a "real life" sample, where the frequency of IIR was not higher than that described in the literature. The form of presentation, behaviour, severity and outcomes were similar to those described in different series.

We emphasize that the low prevalence of IIR corroborates security data, both quantitatively and qualitatively, of the various IV IBD. However, we must emphasize that, despite the expansion of the experience with the use of these drugs, a specialized medical monitoring is still considered essential during infusion, either in the immediate handling of the event, as for the decision of infusion resuming.

Conflicts of interest

IBM received payments for lectures from laboratories Abbvie and Pfizer. RMC participated on boards of Janssen laboratory, and also received payments for lectures from AstraZeneca, Bristol, Roche and Janssen laboratories. The other authors declare no conflicts of interest.

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