Journal of Crohn's and Colitis, 2015, 806–815
doi:10.1093/ecco-jcc/jjv096
Advanced Access publication June 19, 2015
Review Article

Review Article

Infliximab-Related Infusion Reactions: Systematic Review

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Abstract

Objective: Administration of infliximab is associated with a well-recognised risk of infusion reactions. Lack of a mechanism-based rationale for their prevention, and absence of adequate and well-controlled studies, has led to the use of diverse empirical administration protocols. The aim of this study is to perform a systematic review of the evidence behind the strategies for preventing infusion reactions to infliximab, and for controlling the reactions once they occur.

Methods: We conducted extensive search of electronic databases of MEDLINE [PubMed] for reports that communicate various aspects of infusion reactions to infliximab in IBD patients.

Results: We examined full texts of 105 potentially eligible articles. No randomised controlled trials that pre-defined infusion reaction as a primary outcome were found. Three RCTs evaluated infusion reactions as a secondary outcome; another four RCTs included infusion reactions in the safety evaluation analysis; and 62 additional studies focused on various aspects of mechanism/s, risk, primary and secondary preventive measures, and management algorithms. Seven studies were added by a manual search of reference lists of the relevant articles. A total of 76 original studies were included in quantitative analysis of the existing strategies.

Conclusions: There is still paucity of systematic and controlled data on the risk, prevention, and management of infusion reactions to infliximab. We present working algorithms based on systematic and extensive review of the available data. More randomised controlled trials are needed in order to investigate the efficacy of the proposed preventive and management algorithms.

Keywords: Infliximab, infusion reactions, adverse drug reaction, drug hypersensitivity, drug allergy, drug toxicity, inflammatory bowel disease, Crohn's disease, ulcerative colitis

1. Introduction

Infliximab [IFX] is a monoclonal antibody designed to intercept and neutralise tumour necrosis factor alpha [TNFα], a key inflammatory cytokine. Since its introduction in 1998, IFX has revolutionised the treatment of inflammatory bowel disease [IBD]. However, administration of IFX is associated with a well-recognised risk of infusion-related adverse events. The exact aetiology and pathogenesis of those

infusion reactions [IR] are often unclear, and findings regarding their allergic/immune nature are inconsistent. The lack of a mechanism-based rationale for their prevention, combined with the absence of adequate, well-controlled studies, has led to the use of diverse empirical administration protocols, each with its own instructions for infusion rates, choice of preventive medications, and reaction-management algorithms.[1,2,3] We performed a systematic review of strategies for preventing infusion reactions to infliximab and for their management.

2. Methods

We conducted extensive electronic search of English language publications listed in the electronic databases of MEDLINE [source: PubMed database, 1997 through April 2015]. The keywords for the search were arranged in three groups. The first group contained the medical subject headings 'tumor necrosis factor alpha/antagonists and inhibitors' and free-text terms 'infliximab [USAN:INN:BAN]', 'Remicade', 'Avakine', 'HSDB 7850', and 'UNII-B72HH48FLU'. We used set operator AND to combine rendered results with studies identified with the search term 'infusion reactions' and Medical Library Subject heading [MeSH] terms 'adverse drug reaction', 'drug hypersensitivity', 'drug allergy', and 'drug toxicity'. Finally, the search was further narrowed using MeSH terms 'inflammatory bowel disease', 'Crohn's disease', and 'colitis, ulcerative'. We then performed a manual selection of studies that satisfied the following inclusion criteria: [1] comparative studies, meta-analyses, multicentre cohorts, observational studies, randomised controlled trials, and systematic reviews; [2] enrolment of IBD patients treated with infliximab; and [3] availability of data regarding infusion reactions. Exclusion criteria were: studies not published in the English language; publications inaccessible to Tel-Aviv University e-resources; those unrelated to inflammatory bowel disease or irrelevant to the topic; letters and case reports/case series. Reference lists of all relevant articles were searched for further studies. We also searched for relevant abstracts and other material from meetings. Studies concerning the use of IFX in other specialties, such as rheumatology and dermatology, were included if they reported information that was not yet available from IBD studies.

3. Results

The electronic literature search retrieved 203 citations. After application of eligibility criteria, 69 articles remained and were further assessed. We found no randomised controlled trials that pre-defined infusion reaction as a primary outcome. Three RCTs evaluated infusion reaction as a secondary outcome[4,5,6]; another four RCTs included infusion reactions into safety evaluation analysis.[7,8,9] All other reports ranged in level of evidence between meta-analyses [4], multicentre prospective cohorts [8], single-centre cohorts [15], and retrospective trials [21], to systematic reviews [14]; 22 letters and 53 case reports were excluded. An additional 59 articles were excluded for irrelevance, unavailability, or missing premedication and/or the infusion reaction [IR] data. Manual search yielded seven articles for inclusion. This process resulted in 76 articles for inclusion to quantitative analysis of the existing strategies [Figure 1].

4. Terminology and nomenclature

The World Health Organization[10] nomenclature classifies IR to immunoglobulins into two major subtypes, immediate and late, according to the time interval between the infusion and the onset of an infusion-related adverse event.

4.1. Immediate infusion reactions to IFX

Reactions that develop during the course of the infusion or within 1–2 h of its completion are termed immediate-type reactions. Immediate IR are reported in 5–23% of IBD patients participating in large randomised controlled trials involving the originator IFX—Remicade® [Janssen Biotech, Inc., Malvern, PA].[4,5,7,8,9] Comparable rates are reported in unselected patient populations.[2,11,12,13,14,15,16,17,18] Since most immediate reactions occur during the initial infusions,

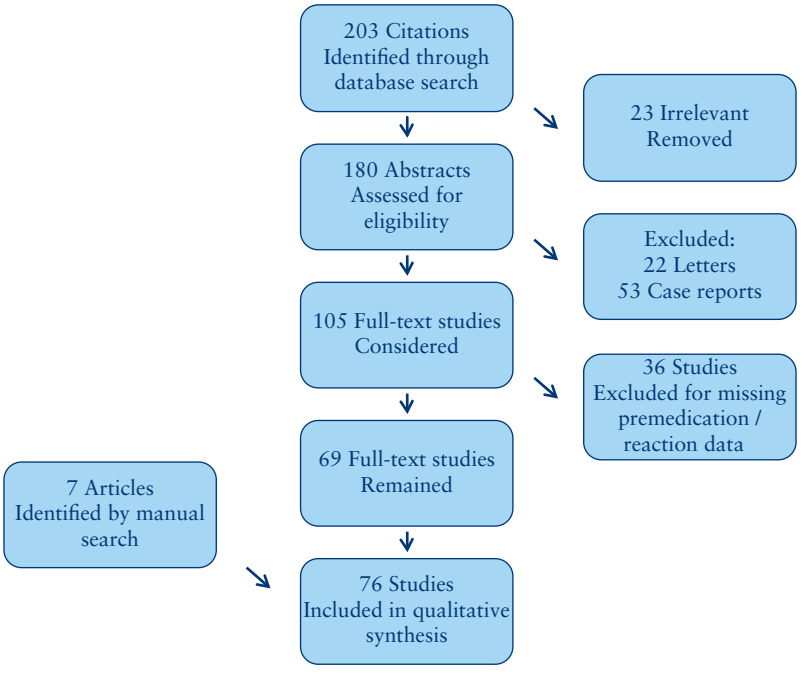

Figure 1. Flow chart of the literature search.

the per-infusion incidence tends to be higher in relatively short-term studies, as opposed to long-term registry reports. The most frequent manifestations of immediate infusion reactions—as reported by a large community registry[19]—are pruritus [22.1% of all reported reactions], flushing [9.9%], dyspnoea [6.2%], chest discomfort [5.9%], hypertension [5.9%], myalgia [5.0%], nausea [4.7%], urticaria [4.7%], headache [4.0%], rash [3.4%], and dizziness [2.8%]. Patients with IBD treated with IFX who develop antibodies toward infliximab [ATI] have a 2-fold risk of acute infusion reactions and a 6-fold risk of serious acute infusion reactions.[20]

4.1.1. Possible aetiologies of immediate infusion reactions to IFX

Possible aetiologies follow.

4.1.1.1. Cytokine-release syndrome

Cytokine release syndrome ['cytokine storm'] is a generalised term originally coined to describe the explosive release of multiple pro- and anti-inflammatory cytokines and vasoactive substances from immune cells, induced by treatment with anti-thymocyte globulin and anti-T-cell antibody muromonab-CD3 [OKT3][21]; the same effect was later reported with other biological agents [eg rituximab[22]]. Underlying mechanisms may include immune cell hyperactivation, direct apoptosis, complement-mediated lysis, and antibody-dependent cellular toxicity.[23] Similar massive, simultaneous release of cytokines from TNF-expressing immune cells affected by IFX has been suggested.[24,25,26] The paradoxical increase in serum TNF observed in the immediate aftermath of initial IFX infusion likely constitutes a reflection of this phenomenon.[27,28,29]

4.1.1.2. True anaphylactic reaction

IgE-mediated [type I] hypersensitivity reactions to IFX may not be as rare as previously thought.[30–32]

4.1.1.3. IgG anaphylaxis

The phenomenon of massive activation of neutrophils by monomeric or aggregated IgG and circulating immune complexes, sometimes referred to as IgG anaphylaxis, has been well described in mice,[33,34] and is presently being extensively researched in humans.[35,36]

4.1.1.4. Complement activation

When IFX is administered to patients with pre-existing anti-IFX antibodies [antibodies toward infliximab, ATI], the resulting circulating IFX-ATI complexes may activate complement, leading to an immediate infusion reaction.[37] Complement activation by IFX molecule aggregates may occur as well.

4.1.1.5. Degranulation

Degranulation of mast cells and basophils, either through IFX targeting of membrane-bound TNF, or via anaphylatoxins [C3a and C5a] that increase in blood as a consequence of complement activation, is thought to account for some of the immediate infusion reactions to IFX.[38]

Clinical manifestations of the immediate IR caused by the aforementioned mechanisms heavily overlap, making it difficult to determine the exact underlying immune/allergic nature of the reaction, based solely on clinical evidence. Some hints, however, can be instructive: IgE-mediated reactions require pre-sensitisation, and should not occur during the first infusion. Wheezing and frank urticaria suggest a massive release of histamine, pointing toward either IgE-mediated or direct mast cell degranulation.[39] Presence of fever, on the other hand, suggests an IR caused by cytokine release.

4.1.2. Severity scale for immediate infusion reactions

In 2006, the National Cancer Institute [NCI] at the National Institutes of Health [NIH] in the USA introduced comprehensive, standardised terminology to grade adverse effects caused by medical therapies.[40] Initially proposed for toxicity related to anti-cancer therapy, the NCI scale has become a cross-field standard in the drug toxicity communication.[14,41] The reactions are divided into five severity grades, ranging from: mild [requires observation only]; through moderate [minimal—usually oral—intervention suffices]; and severe [vital organ involved yet not in life-threatening manner; usually requires parenteral medication]; to life-threatening [multi-system involvement of vital organs, urgent and critical care required]; and death. In terms of immediate infusion reactions, the examples can include: transient flushing or rash [mild reaction]; urticaria/myalgia/drug fever [moderate reaction]; bronchospasm/angioedema/hypotension [severe reaction]; and systemic anaphylactic reaction [life-threatening reaction].

4.2. Late infusion reactions to IFX

Of IBD patients treated by IFX, 1–3% report late-type reactions that first manifest > 24 h post-infusion.[13,31,42,43,44,45] These IR are usually of the serum sickness type and comprise a variety of local and systemic inflammatory responses caused by fixation and activation of complement by antigen [IFX]antibody [ATI] immune complexes deposited in blood vessels, skin, and joint tissue. The risk appears to be increased with episodic ['on demand'] regimens, resumption of IFX infusions after a prolonged drug-free interval, and administration of IFX to patients with high ATI titres.[42,46,47,48,49] The term 'delayed-type hypersensitivity' should probably be reserved for cell-mediated type [Coombs-Gell type IV] reactions: its application to serum sickness [Coombs-Gell type III reactions] may be inappropriate.[10,50]

The quantitative [stoichiometric] relationship between IFX and ATI affects the size of the resulting immune complexes, and their propensity to elicit the inflammatory reaction. Small complexes usually circulate within the bloodstream without triggering inflammation, and larger ones are easily cleared by the reticuloendothelial system. However, intermediate-sized complexes, which develop in the presence of slight antigen [IFX] excess, tend to be deposited in blood vessels and tissues, where they can fix and activate complement, resulting in the attraction of granulocytes and subsequent vascular and tissue damage.

In the absence of pre-existing anti-drug antibodies, serum sickness typically develops 1–3 weeks following administration of the culprit agent.[10] In patients who have been repeatedly sensitised through antecedent exposure to IFX, immune complex-mediated reactions can occur as early as within 24–36 h post-infusion.[51] The most common symptoms of late infusion reactions are pruritic skin eruptions, fever, malaise, and polyarthralgia. Jaw pain is repeatedly mentioned among the features of delayed reaction to biological therapy.[13,15,31,52,53] Although patients may feel very ill, serum sickness is self-limiting, and the symptoms usually subside within days or weeks; its evolution into life-threatening respiratory distress syndrome [ARDS] has been reported in a single, rather unusual case.[54]

4.3. Originator vs biosimilar IFX

CT-P13 [Remsima™/Inflectra™, Celltrion Healthcare Inc., Incheon city, Republic of Korea] is the world's first biosimilar imitation of the originator IFX [Remicade®, Janssen Biotech, Inc., Malvern, PA] and

was recently approved for IBD by the European Medicines Agency [EMA]. Currently, safety [as well as efficacy] data on biosimilar IFX are only available in rheumatology. Infusion-related reactions occurred in 6.6% and 8.3% of rheumatoid arthritis patients for CT-P13 and originator IFX, respectively [6.7% vs 13.3% in the ATI-positive group and 4.2% vs 2.8% in the ATI-negative group].[55] A smaller study in ankylosing spondylitis also showed close similarity between the biosimilar and the originator IFX.[56] Data on IR in IBD are still largely unavailable for CT-P13.

5. IFX infusion protocols

5.1. Graded dose challenge protocol

The manufacturer of the originator IFX recommends that initial [loading] infusions should be administered in a highly controlled manner, beginning with small test doses of the drug, followed by gradual and stepwise escalation of the infusion rate until the full target rate is reached[57] [Table 1].

5.2. Standard [2-h] rate protocol

For patients who tolerate initial [loading] infusions without complications, a simplified single-test dose protocol may be applied[57] [Table 1].

5.3. Accelerated [1-h] rate protocol

In adult patients who tolerate the standard 5 mg/kg maintenance infusions, the infusion time can be further shortened to 60 min,[58,59] conserving both patient time and healthcare resources[60] [Table 1]. Increasing the rate for escalated 10 mg/kg doses over 60 min,[61] and administration of 5 mg/kg infusions over 30 min,[60,62] also appear to be safe.

6. Primary preventive measures

Primary prevention strategies for infusion reactions have been assessed in three target populations[63]: in unselected population [universal prevention]; in populations that were deemed to be particularly predisposed to IR [selective prevention]; and in individuals with warning signs—indicators—of a pending reaction [indicator-based prevention].

6.1. Primary prevention of immediate infusion reactions in unselected population

6.1.1. Gradual increase of infusion rate

The efficacy of an incremental infusion rate schedule to prevent immediate infusion reactions has never been validated in controlled studies. Nevertheless, given the cytokine-release mechanism underlying the majority of such reactions, it would seem to be a prudent approach.

Table 1. Infliximab [IFX] infusion protocols.

Initial [graded challenge] rate schedule*	
Initial 15 min [**'test dose'**]	10 ml/h
Next 15 min	20 ml/h
Next 15 min	40 ml/h
Next 15 min	80 ml/h
Next, until infusion is complete	150 ml/h
Standard [2-] rate protocol*	
Initial 15 min	40 ml/h
Then, until infusion is complete	150 ml/h
Accelerated [1-h] rate protocol*	
Initial 15 min	100 ml/h
Then, until infusion is complete	300 ml/h

*5 mg/kg dose diluted in 250 ml of NaCl 0.9%.

6.1.2. Co-administration of immunomodulators

Co-administration of thiopurine immunomodulators seems to reduce the risk of early infusion reactions during both episodic[64,65] [no longer recommended] and continuous[4,7,66] IFX therapy [Table 2]. Such combination therapy has also been shown to improve the efficacy and reduce the immunogenicity of IFX.[4] Methotrexate has been similarly efficacious in preventing IR in patients that received an episodic single-dose regimen of IFX.[64] Although formally supported as a preventive measure for immediate infusion reactions,[67] the use of immunomodulators should be cautiously weighed against the associated safety concerns, especially risk of infections and lymphomas.[68,69]

6.1.3. Premedication with corticosteroids, antihistamines, and antipyretics

The need for routine premedication with corticosteroids, antihistamines, and/or antipyretics in instances of scheduled maintenance therapy with IFX is controversial,[70] and evidence regarding its efficacy in patients with IBD is relatively limited. Premedication with intravenous corticosteroids may reduce the immunogenicity of IFX but was not directly shown to reduce the risk of IR.[6] Findings for oral corticosteroids[71] or oral antihistamines[72] in patients with arthritis, or the combination of corticosteroids and antihistamines in paediatric patients with IBD/arthritis,[73] were disappointing with respect to IR prevention. Furthermore, robust data prospectively gathered from a large Canadian community registry[19] and from another retrospective study[2] implied that pre-administration of antihistamines, alone or in combination with corticosteroids and/or antipyretics, was paradoxically associated with higher rates of immediate infusion reactions. However, these findings should be interpreted with caution, due to possible selection bias [patients with a perceived higher risk of infusion reactions may have typically received treatment, prior to IFX infusions]. Some intriguing but uncontrolled preventive experience with oral acetylsalicylic acid has been reported in paediatric patients.[74]

6.2. Primary prevention of immediate infusion reactions in selected populations

Episodic ['on demand'] IFX treatment is associated with the formation of neutralising antibodies against infliximab, and is therefore not recommended.[42] However, elective, temporary [eg pregnancy- or surgery-related] interruption of IFX therapy is not unusual. Late immune-related adverse events such as serum sickness were repeatedly reported when infusions were resumed following a prolonged [more than 12-week] drug-free interval.[15,48,65] Data on the occurrence of immediate infusion reactions are inconsistent. A significant increase in the frequency of serious immune-related adverse events was observed in some series,[65] but not in others.[75] Targeted prophylactic premedication with corticosteroids, antihistamines, and antipyretics has become common practice in such instances,[70,76] but its efficacy was recently called into question by findings from a large retrospective study,[65] though never validated in

Table 2. Effect of concomitant treatment with thiopurines on the incidence of infusion reactions [IR] to infliximab [IFX] [SONIC trial].

Incidence	IFX	IFX + thiopurines
IR per patient	16.6%	5.0%
IR per infusion	4.6%	1.0%

controlled studies. According to this study, co-administration of immunomodulators was the only preventive measure associated with a reduction of IR frequency [from 34% to 12%].

Patients with atopy constitute another selected population theoretically at risk for IR. Treatments that tend to activate complement result in rise of anaphylatoxins C3a and C5a, triggering degranulation of mast cells and basophils. This phenomenon may be exaggerated in atopic patients; asthma and atopic dermatitis are often regarded as indications for premedication prior to administration of intravenous iron[77] and iodine contrast.[78] Activation of complement by circulating immune complexes and aggregates of IFX molecules may theoretically occur during some IFX infusions. However, available data suggest that patients with severe atopic dermatitis[79] or patients with variety of atopic conditions[80] are not at risk for an increased rate of infusion reactions to IFX.

6.3. Indicator-based primary prevention of immediate infusion reactions

The presence of ATI is associated with an increased risk of an immediate infusion reaction during both episodic and scheduled administration of IFX.[20] One out of six ATI-positive patients will display an infusion reaction when treated with IFX[20]; the underlying mechanism is unclear. ATI are frequently associated with inadequate trough levels of IFX, and the re-emergence of circulating cells bearing the target antigen [TNF]. Administration of IFX in this setting might trigger cytokine release from these cells, thereby provoking an infusion reaction.[65,81,82] Activation of the immune system by circulating IFX-ATI immune complexes constitutes another proposed mechanism.[37]

It is unclear if rising titres of ATI [or the resulting progressive loss of response] can serve as an indicator of a pending infusion reaction. Assessment of ATI titres has been proposed as a risk stratification strategy for infusion reactions,[65,83] but its positive predictive value has thus far been insufficient to draw operative conclusions.[20,42] Furthermore, the absence of ATI does not preclude infusion reaction.[84,85] Studies of patients with rheumatological diseases[32,83] suggested that the assessment of anti-IFX IgE levels could serve as a means to determine the risk of severe infusion reactions to IFX. However, this approach failed to show preventive benefit in patients with IBD.[85]

Coupled with the questionable efficacy of prophylactic premedication, its routine use in patients with ATI may therefore not be justified.

6.4. Primary prevention of late reactions

It would appear that late infusion reactions are triggered by the binding of IFX by ATI, followed by deposition of the resulting ATI-IFX immune complexes and fixation of complement. The reintroduction of IFX after a drug holiday,[42,46,47,48,49] and the presence of ATI,[8,86] have been suggested as risk factors for serum sickness-like reactions, but the relationship is not always consistent.[42,47,81] The exact stoichiometric conditions that result in the production of intermediate-sized immune complexes are difficult to predict, as only one out of every 22 ATI-positive patients will develop a late reaction to IFX treatment.[20] No operative conclusions regarding the necessity for preventive measures can be drawn from either the presence or the exact titre of ATI.[42]

7. Management of ongoing infusion reactions

7.1. Management of ongoing immediate infusion reactions to IFX

There are no controlled trials to guide the management of IR to IFX. Therapeutic recommendations are based mainly on case reports and expert opinion.[31,51,87,88,89,90,91,92] The majority of IFX-related infusion reactions are thought to result from rapid, infusion rate-related cytokine release from the affected immune cells. In these cases, temporary attenuation of the infusion rate is regarded as the most effective, and often the only, required intervention.[31,91] However, the appearance of hives, bronchospasm, and vascular compromise should raise suspicions of an IgE-mediated anaphylactic reaction,[39] which warrants prompt interruption of the infusion, intramuscular administration of epinephrine, and a further immunological work-up.[91] In general, intervention is dictated by severity of the reaction.[40] Temporary attenuation of the infusion rate is often the only intervention required in cases of mild and transient immediate infusion reactions. In cases of moderate infusion reactions, temporary interruption of the infusion is necessary in most instances, together with [usually oral] administration of medications to control the symptoms.[31,51,87,88,89,90,91,92] The simultaneous involvement of multiple vital organ systems, especially if complicated by respiratory compromise or/and vascular collapse, is a true medical emergency. Regardless of the exact aetiology, prompt initial treatment is crucial. In these extreme, albeit relatively infrequent, scenarios, the importance of the infusion team's familiarity with the simple and stepwise management algorithm cannot be overemphasised. The recently published guidelines of the World Allergy Organization [WAO][93,94] stress the role of epinephrine as a principal, potentially life-saving intervention. A suggested algorithm for the management of ongoing immediate infusion reactions is depicted in Figure 2.

7.2. Management of late infusion reactions to IFX

The relatively rare occurrence of late infusion reactions precludes randomised clinical trials as to how they should be managed. Antihistamines are often suggested for symptomatic relief of pruritus; acetaminophen serves for symptomatic relief of low-grade fever and arthralgias. Patients with higher fever, severe arthralgias/arthritis, or extensive rash/pruritus often require a short course of oral corticosteroids; intravenous corticosteroids can be considered in acutely ill patients.[89]

8. Secondary preventive measures

Acute infusion reactions tend to recur in about a third of subsequent IFX infusions.[19,95] Even when not severe, infusion reactions are important immunological events as they often represent warning signs for emergence of ATI and consequent decline of drug levels and loss of clinical response.[20,96,97] In this regard, IR, and especially recurrent IR, should prompt ATI and IFX trough level determination.

8.1. Secondary prevention of immediate infusion reactions to IFX

A suggested secondary prevention protocol is outlined in Figure 3 and may include the following measures.

8.1.1. Co-administration of immunomodulators

Although a small retrospective study[98] showed the addition of immunomodulators to ongoing monotherapy with IFX was able to eliminate pre-formed neutralising ATI and restore clinical response to IFX, it is still unknown whether this approach is effective in preventing recurrent IR. As noted above, the possible benefits of this combination therapy have to be carefully weighed against associated long-term safety concerns.

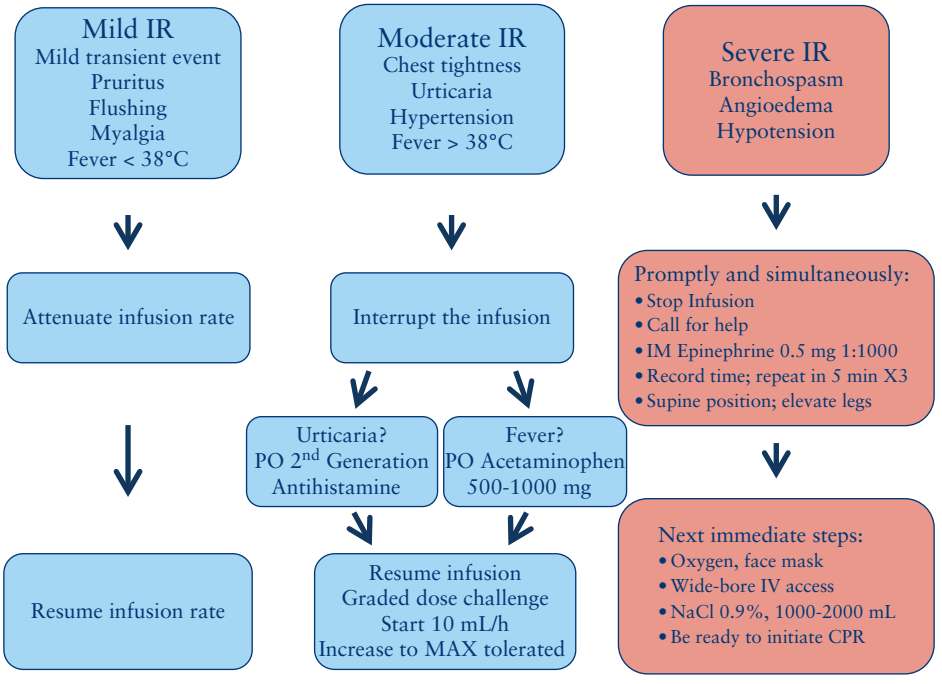

Figure 2. Suggested management algorithm for infusion reactions.

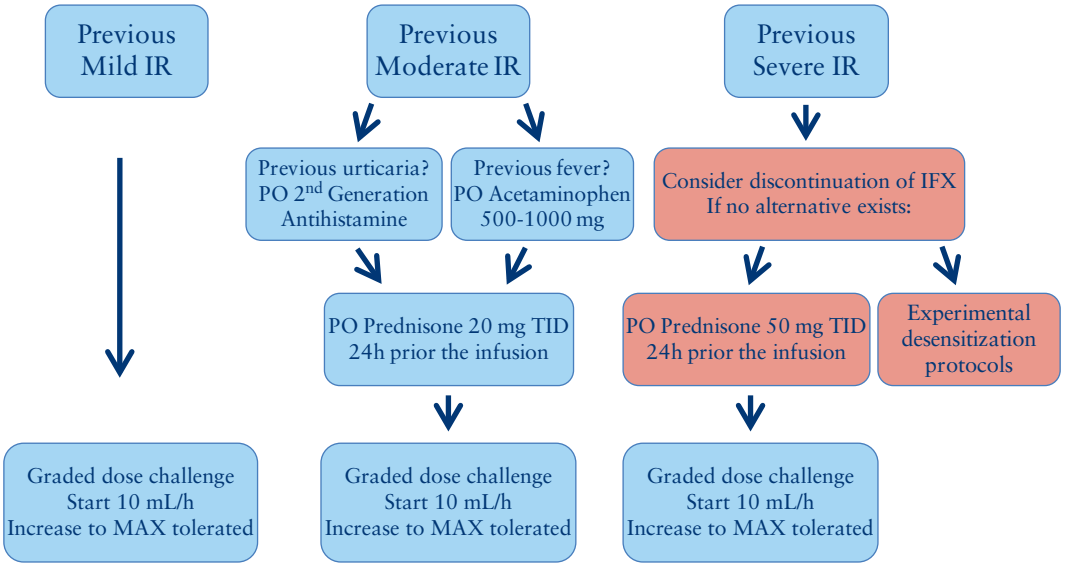

Figure 3. Suggested premedication protocol in patients with prior infusion reactions.

8.1.2. Graded dose challenge

Experts suggest the use of graded drug challenge during resumption of IFX infusions, in patients with prior infusion reactions.[31,87,88,91] This precautionary measure, originally derived from infusion practices for 5-fluorouracil and vancomycin,[31,99,100] consists of incremental administration of small test doses of IFX, followed by gradual, stepwise escalation of the infusion rate until the full target rate [or maximum tolerated rate] is reached [Table 1]. Clinicians assume that if cytokine release underlies the majority of cases of immediate infusion reaction, then any infusion reactions provoked by the smaller test doses would be milder, and easier to manage. Although this assumption has never been formally subjected to controlled validation, in practice, graded dose challenge is widely accepted by most infusion centres.

8.1.3. Premedication with corticosteroids, antihistamines, and/or antipyretics

Numerous premedication protocols, most of them adapted from administration practices for iodine contrast media,[51,90] have been empirically employed in IFX infusion centres to prevent recurrence of moderate infusion reactions. None of these has ever been subjected to controlled validation. In a small retrospective study of paediatric patients,[101] the re-treatment of children who had suffered from infusion reactions without prophylactic administration of anti-allergic medications was associated with a significant [50%] likelihood of recurrent infusion reactions. The probability of recurrent infusion reactions tended to be lower in patients premedicated with antihistamines, antipyretics, or corticosteroids. In contrast, others

found that in the adult population, premedication was not associated with a reduced risk of recurrent infusion reactions.[13] Nevertheless, the prophylactic pre-administration of antihistamines, antipyretics, and/or corticosteroids is frequently suggested,[88,89,91] albeit with no widespread agreement on the exact criteria and indications, choice of specific medications, dose, or administration route.[31,87,88,89,91] The main argument in favour of premedication is that it may be justified in patients with a history of moderate infusion reactions, even if a large number of patients may need to be treated for even one to benefit. Severe and potentially life-threatening acute generalised infusion reactions usually warrant discontinuation of treatment. If no reasonable therapeutic alternative exists, pretreatment with corticosteroids and antihistamines, and rapid desensitisation by an experienced clinical immunologist/allergist, could be considered.

8.1.4. Desensitisation

Desensitisation to a specific medication was originally described for IgE-mediated anaphylactic reactions, and involves graded administration of the offending drug, starting with extremely low doses [1:1000 and 1:100 dilutions], followed by slow, stepwise dose escalations, until the target dose is clinically tolerated. Consecutive low-level, subthreshold antigen stimulation seems to render tissue mast cells and probably circulating basophils specifically unresponsive to the offending drug, but not to other stimuli. Internalisation and down-regulation of the high-affinity receptor on the Fc fragment of IgE [FcεRI] are among the mechanisms believed to underlie this effect. Slow depletion of mast cell granules may also take place. Desensitisation protocols are in routine use in antibiotic, anticancer, and biological treatments [including the monoclonal agents rituximab and trastuzumab]. They make possible the administration of life-saving therapies to patients with a history of severe immediate infusion reactions.[102] Experience with desensitisation to IFX is limited to case reports and small series studies.[38,103,104,105] The reported rate of breakthrough reactions in these series reached 29%,[103] remarkably similar to the reaction recrudescence rate observed without desensitisation.[19] However, these reactions tended to be significantly milder and, in most cases, allowed for successful continuation of the infusion.

8.2. Secondary prevention of late infusion reactions to IFX

Late infusion reactions depend on unique stoichiometric conditions, resulting in the production of intermediate-size immune complexes. Such conditions may not recur after subsequent infusions.[31,106] Genuine preventive interventions that preclude the formation of immune complexes of reactogenic size must focus on moderation of post-infusion IFX levels [eg by dose escalation, or by split administration of the unchanged dose,[51,90]] or on elimination of neutralising ATI [eg. through addition of immune modulators to ongoing IFX monotherapy[98]]. Neither technique has ever been properly evaluated in this setting, and all therefore are still considered theoretical. Premedication with anti-inflammatory/antihistamine medications is not a truly preventive measure. Rather, it is intended to overcome associated signs and symptoms of the anticipated [recurrent] infusion reaction.[107] As such, premedication has already been covered in the management chapter.

9. Conclusions

There is still paucity of systematic and controlled data on the risk, prevention, and management of infusion reactions to infliximab. We present working algorithms based on systematic and extensive review of the available data. More randomised controlled trials are needed in order to investigate the efficacy of the proposed preventive and management algorithms.

Funding

The Open Access fee for this article was covered by Janssen Israel. Lev Lichtenstein, Yulia Ron, and Batia Weiss received consulting fees from Janssen during the conduct of the study.

Conflict of Interest

Lev Lichtenstein reports lecturer and consulting fees from AbbVie, research support from Janssen, a non-financial support from Takeda, all outside the submitted work, and consulting fees from Janssen during the conduct of the study. Yulia Ron reports consulting fees from Janssen during the conduct of the study. Shmuel Kivity has nothing to disclose. Shomron Ben-Horin reports consulting and advisory board fees and/or research support from AbbVie, MSD, Janssen, Takeda, and Celltrion, all outside the submitted work. Eran Israeli has nothing to disclose. Gerald M Fraser has nothing to disclose. Iris Dotan reports advisory board fees from AbbVie, Janssen, Takeda, Genentech, and Pfizer, and lecturer fees from AbbVie, Janssen, Ferring, Falk Pharma, Given Imaging-Covidien, and MSD, all outside the submitted work. Yehuda Chowers reports consulting fees from Abbvie, Janssen, Takeda, and Pharmacosmos, and research support from Abbvie, and Janssen, all outside the submitted work. Ronit Confino-Cohen has nothing to disclose. Batia Weiss reports lecturer fees from Janssen, outside the submitted work, and consulting fees from Janssen during the conduct of the study.

Author Contributions

Lev Lichtenstein, Yulia Ron, Shmuel Kivity, Ronit Confino-Cohen, and Batia Weiss conducted the literature search, and contributed to study design, data collection, data analysis, data interpretation, writing, and revision of the manuscript, and figure creation. Shomron Ben-Horin, Eran Israeli, Gerald M Fraser, Iris Dotan, and Yehuda Chowers contributed to study design, data analysis, data interpretation, writing and revision of the manuscript and figure creation. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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