Digestive and Liver Disease 51 (2019) 484–488

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Premedication as primary prophylaxis does not influence the risk of acute infliximab infusion reactions in immune-mediated inflammatory diseases: A systematic review and meta-analysis

Mathurin Fumery[a,*,1], Marion Tilmant[a,1], Clara Yzet[a], Franck Brazier[a], Julien Loreau[a], Justine Turpin[a], Jean Philippe Le Mouel[a], Vincent Goeb[b], Eric Nguyen-Khac[a], Siddarth Singh[c], Jean-Louis Dupas[a], Momar Diouf[d]

[a] Gastroenterology, Amiens University Hospital, Université de Picardie Jules Verne, Amiens, France, France
[b] Rheumatology, Amiens University Hospital, Université de Picardie Jules Verne, Amiens, France
[c] Division of Gastroenterology, Department of Medicine, UC San Diego Health System, La Jolla, USA
[d] Department of Biostatistics, Amiens University Hospital, Amiens, France

ARTICLE INFO

Article history:
Received 27 August 2018
Accepted 5 December 2018
Available online 13 December 2018

Keywords:
Infliximab
IMIDs
Inflammatory bowel disease
premedications

ABSTRACT

Introduction: Up to 25% of patients treated with infliximab experience hypersensitivity reactions. Prophylactic premedication prior to infliximab infusion, comprising corticosteroids and/or antihistamines, is widely used in clinical practice but its efficacy has recently been called into question due to the lack of pathophysiological rationale and validation by controlled trials.
Materials and methods: We conducted a comprehensive literature search of multiple electronic databases from inception to June 2017 to identify studies reporting the impact of corticosteroid and/or antihistamine premedication on the risk of acute (<24 h) hypersensitivity reaction to infliximab in immune-mediated inflammatory diseases (IMIDs). Random-effects meta-analysis was performed.
Results: Ten studies, eight observational studies and two randomized control trials, were identified including a total of 3892 patients with IMIDs, and 1,385 patients with IBD. Corticosteroid premedication was not associated with a decreased risk of hypersensitivity reaction in either IMIDs (7 studies; OR, 1.07, 95%CI, 0.64–1.78; $I^2 = 57.5\%$) or IBD (3 studies; OR, 1.04, 95% CI, 0.52–2.07; $I^2 = 57\%$). Antihistamine premedication was not associated with a decreased risk of hypersensitivity reaction in IMIDs (3 studies: OR, 1.39, 95% CI, 0.70–2.73; $I^2 = 85\%$). The combination of corticosteroids and antihistamines did not decrease the risk of acute infliximab infusion reaction in IMIDs (6 studies; OR, 2.12, 95% CI, 0.61–7.35; $I^2 = 94\%$), but was associated with an increased risk in IBD (4 studies, OR, 4.17, 95% CI, 1.61–10.78; $I^2 = 77\%$).
Conclusion: Corticosteroid and/or antihistamine premedication is not associated with a decreased risk of acute hypersensitivity reactions to infliximab in patients with IMIDs. We believe that these premedications should no longer be part of standard protocols.

1. Introduction

Infliximab (IFX), a chimeric monoclonal IgG1 antibody directed against tumor necrosis factor, has revolutionized the treatment of immune mediated-inflammatory diseases (IMIDs), including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Pso) and psoriatic arthritis. However, administration of IFX is associated with a well-recognized risk of acute infusion reactions, which are reported to occur in about 1–6% of infusions and 5–27% of patients [1–5]. Acute infusion reactions associated with IFX range from mild reactions, including fever and chills, dyspnea, pruritus, or urticaria, to severe reactions including anaphylaxis, convulsions, and hypotension. The pathogenesis of these acute infusion reactions remains unclear, with inconsistent findings concerning their allergic/immune nature [5].

Prophylactic corticosteroid and/or antihistamine premedication is widely used in clinical practice, but its efficacy has recently been called into question because of the lack of a pathophysio-

* Corresponding author at: Service Hépato-Gastroentérologie, CHU Amiens Picardie, Université de Picardie Jules Verne, Site Sud - D408, 80054 Amiens, France.
E-mail address: Fumery.mathurin@chu-amiens.fr (M. Fumery).
[1] These authors contributed equally.

https://doi.org/10.1016/j.dld.2018.12.002
1590-8658/

logical rationale for their prophylactic effect. This premedication has been evaluated in two randomized controlled trials [6,7]. However, a substantial proportion of healthcare providers still use these drugs before every IFX infusion. In a recent survey, 70% of gastroenterologists reported using an antihistamine and 50% reported using corticosteroids before each infliximab infusion [8]. However, patients with IMIDs receive IFX as a steroid-sparing agent, and, although rare, negative effects of short-term administration of intravenous corticosteroid premedication have been reported [9].

In order to more clearly understand the impact of antihistamine or corticosteroid premedication on the risk of IFX-related acute infusion reactions, we therefore conducted a systematic review of the published data and conducted a meta-analysis.

2. Methods

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) standards, and according to a previously published protocol (registered at the International Prospective Register of Systematic Reviews, PROSPERO CRD42018086014).

2.1. Study selection

Studies meeting the following criteria were included: (a) randomized controlled trials, observational cohort or case-control studies in (b) adult patients (c) with a diagnosis of RA, AS, Pso, psoriatic arthritis, Crohn's disease or ulcerative colitis, (d) reporting IFX-related acute infusion reactions; (e) patients treated with corticosteroid and/or antihistamine premedication included matched controls; (f) reporting relative risks (RR), hazard ratios (HR), odds ratios (OR), or standardized incidence rates with 95% confidence intervals (CI) or providing data allowing calculation of these parameters. Inclusion was not otherwise restricted by study size, language, or publication type. In the case of multiple publications based on the same cohort, data from the most recent comprehensive report were included.

2.2. Search strategy

We conducted a comprehensive search of multiple electronic databases from inception to June 31, 2017 concerning adult patients, with no language restrictions using the following search terms: ("IBD" OR "IMIDs" OR "AS" OR "RA" OR "RA" OR "Pso") AND ("IFX") AND ("infusion reaction") OR ("premedication" OR " steroids" OR "antihistamines"). The databases included MEDLINE, and EMBASE. Conference abstracts (Digestive Disease Week, United European Gastroenterology Week, European Crohn and Colitis Organization congress, American College of Rheumatology, European League Against Rheumatism, American Academy of Dermatology and European Academy of Dermatology and Venereology annual meetings) from 2015 to 2017, and the references of the selected articles and review articles on the topic were also manually searched for additional studies, with no language restrictions. Two reviewers (MF and MT) independently assessed the title and abstract of studies identified in the primary search for inclusion, and the full texts of the remaining articles were examined to determine whether or not they met the inclusion criteria. Any discrepancy in article selection was resolved by consensus, and discussion with a third reviewer.

2.3. Data extraction and definition

Two authors (MF and MT) independently extracted data on: (a) study characteristics: primary author, study period/year of publication, country of the study population, population source, number of patients and/or number of IFX infusions included, duration of follow-up; (b) population characteristics: type of IMIDs; number of IFX infusions; (c) characteristics of infusion reactions: definition of infusion reaction, number of infusion reactions, number of severe infusion reactions; (d) infusion reaction: HRs, ORs, RRs, rate ratios for each premedication and comparator, together with their 95%CI, were recorded. When only incident outcomes were reported, the numbers of events in the groups compared were extracted. When several adjustment models were reported, the most adjusted estimates were used in the analysis.

2.4. Data extraction and quality assessment

Data on study-, patient-, infusion-related characteristics, as well as outcomes of interest from the studies included were extracted in a standardized data collection form (MF, MT). Any discrepancies were addressed by joint review of the original article. The methodological quality of studies was assessed using the National Institute of Clinical Excellence (NICE) quality assessment checklist.

2.5. Outcome assessed

The outcome measure was an acute infusion reaction, defined by any adverse event occurring during the infusion or within 24 h post-infusion, in patients receiving premedication with (a) corticosteroids, (b) antihistamines or (c) a combination of corticosteroids and antihistamines.

2.6. Statistical analysis

Assuming inherent heterogeneity between studies, we used the random-effects model described by DerSimonian and Laird to calculate pooled OR (and 95% confidence intervals [CI]) of infusion reactions [10]. We assessed heterogeneity between study-specific estimates using the inconsistency index (I^2), with cut-offs of <30%, 30%–59%, 60%–75% and >75% to suggest low, moderate, substantial and considerable heterogeneity, respectively [11]. A p value < 0.10 was considered to indicate statistically significant heterogeneity using Cochran's Q test. Small study effects were assessed qualitatively using funnel plot asymmetry and quantitatively using Egger's regression test [12]. In order to explain heterogeneity, the association between the magnitude of OR and study characteristics was assessed by meta-regression; a p value < 0.10 was considered to be statistically significant. All statistical analyses were performed with R-Studio software (Version 1.0.143) and SAS® software (version 9.4, SAS Institute Inc., Cary, NC).

3. Results

3.1. Literature search

Nine of the 5150 studies identified by the search strategy met the inclusion criteria [1,6,7,13–18]. One abstract was also identified from conference proceedings [19]; a total of 10 studies were therefore included for quantitative analysis. **Supplementary** Fig. 1 shows the study selection diagram.

3.2. Characteristics and quality of the studies included

The characteristics of the studies included are described in Table 1. Ten studies, including a total of 3892 patients with IMIDs and 1935 patients with IBD, comprising a median of 1667 (IQR: 642–3,892) IFX infusions, were included. The acute infusion reaction rate ranged from 2 to 28%. Five studies were conducted in Europe and five were conducted in North America. Two studies were randomized controlled trials and eight were observational

Table 1
Study characteristics. Abbreviations: RA, Rheumatoid arthritis; AS, Ankylosing spondylitis; Pso, psoriasis; RP, Psoriatic arthritis.

Study	Country	Study period	Number of patients (n)	Number of infusion (n)	Type of IMIDs	Patients with reaction	Infusion with reaction
Bartoli et al. [13]	Florence, Italy	2002–2014	105	/	RA, AS, PA	30	30
Choquette et al. [1]	Canada	2005–2012	1632	24 852	IBD, RA, AS, PA, Pso	201	322
Baert et al. [14]	Leuven, Belgium	/	128	/	IBD	25	/
Lee [15]	Edmonton, Canada	2009	415	2165	IBD, RA, AS, Pso	/	40
Van Assche et al. [16]	Belgium, Leuven	2008	177	177	IBD	4	4
Keshavarzian et al. [17]	USA	2005	447	6469	IBD	90	226
Farrell et al. [6]	Boston, USA	2000–2001	80	159	IBD	16	/
Sany [7]	France	2001–2002	355	1667	RA	48	63
Duron et al. [18]	Clermont, France	2008–2013	80	1107	IBD	23	38
Gold et al. [19]	NYC, USA	2008–2016	473	5620	IBD	/	94

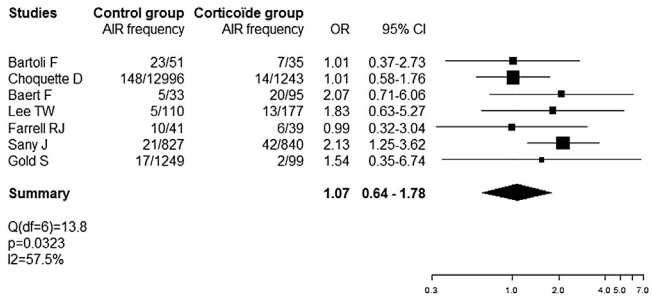

Fig. 1. Impact of corticosteroid premedication on infliximab acute infusion reaction in immune-mediated inflammatory diseases. *AIR: acute infusion reaction; OR, Odds Ratio; CI, confidence interval.*

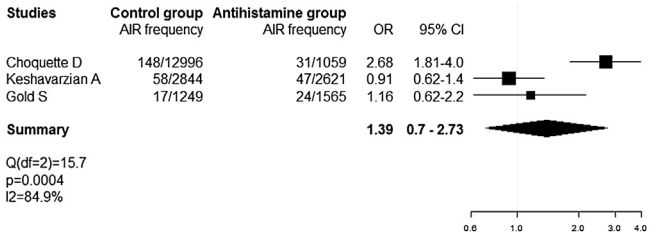

Fig. 3. Impact of antihistamine premedication on infliximab acute infusion reaction in immune-mediated inflammatory diseases. *AIR: acute infusion reaction; OR, Odds Ratio; CI, confidence interval.*

studies, including two multicenter studies and three prospective studies. Three studies included patients presenting various IMIDs, three studies only included patients with IBD and one study only included patients with RA. Seven studies evaluated the impact of corticosteroid premedication, three evaluated the impact of antihistamine premedication and six studies evaluated the impact of combinations of corticosteroids and antihistamines. The quality of the studies included, comprising six high-quality studies and four good-quality studies, is shown in **Supplementary** Table 1.

3.3. Value of corticosteroid premedication

Seven studies were included. On meta-analysis, corticosteroid premedication was not associated with a decreased risk of acute infusion reactions in IMIDs (OR, 1.07; 95% CI, 0.64–1.78) (Fig. 1) with moderate heterogeneity (I^2 = 57.5%). Similar results were obtained when the analysis was confined to the three studies including IBD patients (OR, 1.04; 95% CI, 0.52–2.07), (I^2 = 85%) (Fig. 2). One study evaluated impact of betamethasone premedication in patients with RA and failed to demonstrate any protective effect (14.3% vs 10.3%, p = 0.28) [7].

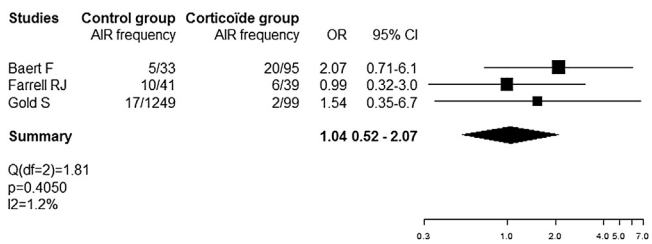

Fig. 2. Impact of corticosteroid premedication on infliximab acute infusion reaction in inflammatory bowel disease. *AIR: acute infusion reaction; OR, Odds Ratio; CI, confidence interval.*

3.4. Value of antihistamine premedication

Three studies, one including patients with IMIDs and two including patients with IBD, were included. On meta-analysis, antihistamines was not associated with a decreased risk of acute infusion reactions in IMIDs (OR, 1.39; 95% CI, 0.70–2.73) (Fig. 3) with considerable heterogeneity (I^2 = 84.9%).

3.5. Value of combined corticosteroid and antihistamine premedication

Six studies were included; four only including patients with IBD and two including patients IMIDs. On meta-analysis, combined corticosteroid and antihistamine premedication was not associated with a decreased risk of acute infusion reactions in IMIDs (OR, 2.12; 95% CI, 0.61–7.35) with considerable heterogeneity (I^2 = 94%). An increased risk of acute infusion reactions was observed in IBD patients following this form of premedication (OR, 4.17; 95% CI, 1.61–10.78), (I^2 = 77.2%).

Using meta-regression, the type of premedication (antihistamines and corticosteroids vs. corticosteroids, OR = 2.56 [0.89; 7.31]; p = 0.07) and the duration of follow-up (OR = 1.08 [0.97; 1.21]; p = .16) explained part of the observed heterogeneity. Funnel plots were generated to assess publication bias. The symmetrical distribution of the studies on the funnel plot suggested that no publication bias was observed for the analysis of corticosteroid premedication (p = 0.61) or antihistamine premedication (p = 0.78). In contrast, publication bias was suspected for corticosteroid and antihistamine premedication (p = 0.0015).

4. Discussion

IFX therapy is largely prescribed worldwide for the treatment of IBD, RA, AS, Pso and psoriatic arthritis. Administration of IFX is associated with a well-recognized risk of acute infusion reactions. IFX is a chimeric monoclonal antibody with higher immunogenicity than humanized monoclonal antibodies [20]. A strong relationship has been described between blood levels of anti-infliximab antibody, observed in about 20% of patients, and acute infusion

reactions [14,21]. Corticosteroid premedication is widely used in clinical practice to decrease the formation of anti-drug antibodies, and antihistamines are used to prevent or reduce allergic reactions [8]. However, the benefit of these premedications remains a subject of debate. This meta-analysis of ten studies did not demonstrate any benefit of premedication with corticosteroids or antihistamines alone, or in combination, on the risk of IFX-related acute infusion reactions in patients with IMIDs. Two placebo-controlled trials evaluated premedication with intravenous corticosteroids to prevent the incidence of acute infusion reactions. Farrell et al. randomized 80 patients with CD to hydrocortisone 200 mg or placebo before their first and subsequent IFX infusions. All patients in this trial received episodic/on-demand IFX therapy, a strategy associated with the development of high levels of immunogenicity and a high rate of acute infusion reactions [6]. The rate of infusion reactions was not significantly different between the two groups. The trial by Sany et al. was a 36-week trial, in which 355 patients with RA treated by IFX in induction and maintenance therapy were randomized to receive either placebo or intravenous betamethasone premedication. The incidence of acute infusion reactions was higher in the betamethasone group (5.0% vs 2.5%, respectively, $p = 0.05$) [7].

The role of intravenous hydrocortisone premedication to prevent the formation of anti-IFX antibodies and infusion reactions remains unclear. In the randomized controlled trial by Farrell et al., hydrocortisone premedication significantly reduced anti-infliximab antibody levels, but did not totally eliminate their formation or the development of infusion reactions [7].

This meta-analysis showed an increased rate of acute infusion reactions in patients receiving combined corticosteroid and antihistamine premedication, which could be the result of a selection bias whereby patients at high risk of acute infusion reactions were more likely to receive double premedication.

Another factor consistently reported as being associated with IFX-related acute infusion reactions is drug holiday. The present study did not specifically study the impact of premedication in this particular population. Concomitant immunosuppressive agents are the only consistently reported protective factors for prevention of IFX-related acute infusion reactions. Significantly fewer infusion reactions occurred in patients receiving concomitant immunosuppressive therapy compared to patients not receiving concomitant immunosuppressive therapy for RA or IBD [5,14]. Combination therapy has also been shown to improve the efficacy and reduce the immunogenicity of IFX [22–25]. Many experts recommend an incremental infusion rate schedule to prevent immediate infusion reactions. This strategy is based on the cytokine release mechanism underlying most of these reactions. Although it has never been validated, this strategy would appear to be a reasonable approach for both primary and secondary prevention [6].

This study presents several limitations. Firstly, differences in the definition of acute infusion reaction were observed between studies. Secondly, some of the studies included patients with a history of acute infusion reaction (secondary prevention). Thirdly, significant heterogeneity was observed across analyses. To evaluate the possible impact of these important limitations, we performed meta-regression to identify prespecified sources of heterogeneity and used a pre-determined definition of acute infusion reaction.

In conclusion, this meta-analysis did not demonstrate any benefit of premedication by corticosteroids, antihistamines or combination of the two on the risk of IF-related acute infusion reaction. These premedications increase the total time spent in the infusion unit and the overall cost of injection. They are also time-consuming for these often young patients, at work or at school. Moreover, some premedications, such as corticosteroids, could have side effects despite low exposure. We believe that these premedications prior to IFX infusion should no longer be part of standard protocols.

Disclosures

MF, lecture fees or consultant fees from MSD, Abbvie, Takeda, Ferring, Hospira and Boehringer. JL, lecture fees from Abbvie. SS, Research grants from Pfizer and AbbVie, Consulting fees from AbbVie, Takeda, Pfizer, AMAG Pharmaceuticals

Conflict of interest

None declared.

Funding

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.12.002.

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