The effect of pre-operative biologic drugs on complications and function after restorative proctocolectomy with primary ileal-pouch formation: systematic review and meta-analysis

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Running title: anti-TNF-α and complications after IPAA

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Conflicts of Interest and Source of Funding: none

Abstract

Background: Debate exists concerning the presumed risk of postoperative complications in ulcerative colitis(UC) patients receiving preoperative infliximab(IFX). Meta-analyses are contrasting due to many confounders included into analysis. Our aim was to determine the impact of IFX on pouch-related postoperative complications in UC patients undergoing surgery with primary ileal pouch-anal anastomosis(IPAA).

Methods: We performed a systematic review to identify studies comparing the outcomes of patients undergoing surgery for UC with or without previous IFX exposure. The primary endpoints were: a) early IPAA-related complications after surgery with primary pouch formation, and b) those occurring after ileostomy closure. Secondary endpoints were the effects of IFX on total,infectious and non-infectious complications in UC patients undergoing any type of surgery. Results are reported as pooled odds ratio(OR)with 95%confidence intervals(CI).

Results: Seven papers including 162 patients receiving biologics and 468 controls all undergoing primary pouch formation were included for the primary aim. Patients receiving IFX were more likely developing early(OR=4.12 95%CI 2.37-7.15,P<0.001) and post-ileostomy closure (OR=2.27, 95%CI 1.27-4.05,P=0.005)IPAA-related complications. Numbers-needed-to-harm(NNH) were 5and4,respectively. Having received at least 3 IFX effusions increased the risk of early complications(OR=9.59, 95%CI 2.92-31.44,P=0.0002), while an interval <12weeks since last effusion did not (OR=2.35, 95%CI 0.98-5.64,P=0.06).

Meta-analyses of fourteen studies reporting on any type of surgery found that IFX showed a trend toward higher total and infectious complications,but no significant differences were

observed. Biologics were associated with lower surgical site infection(SSI)(OR=0.67, 95%CI 0.45-0.99, P=0.04).

Conclusions: IFX exposure increases early pouch-specific complications as well as complications after ileostomy closure in UC. Avoiding primary pouch formation could be a prudent approach.

Key-words: restorative proctocolectomy; ulcerative colitis; anti-TNF-α; inflammatory bowel disease; Infliximab; postoperative complications

Introduction

Anti-tumor necrosis factor (TNF) antibodies are a viable treatment in refractory ulcerative colitis (UC) patients [1]. Infliximab (IFX) has been used for over a decade, and it is effective in inducing remission of acute colitis, even if the rate of colectomy seems to be similar to that of the pre-biological era in the long-term [2,3]. However, these agents have been associated with several undesired early and late side-effects, i.e. increased risk of infections, and, in the long-term, possible increased incidence of lymphoprolipherative disorders [4]. These observations should be posed into perspective when considering anti-TNF-α in UC presenting in very young as well as in elderly, frail patients.

Restorative proctocolectomy, consisting of total proctocolectomy with ileal pouch-anal anastomosis (IPAA), is the procedure of choice for the treatment UC refractory to medical treatment or when dysplasia or cancer occur. Approximately 10-30% of UC patients will need surgery during life, and younger patients show almost doubled risk of losing response to medical treatment [3,5,6]. Nowadays surgery is often performed while patients are being treated with biological drugs. However, despite several meta-analyses have been reported concerning the effect of biologic agents on the surgical risk of IBD patients, data concerning the influence of IFX on perioperative and postoperative complications after pouch formation are still conflicting [2,7-9]. Nonetheless, a potential impact on postoperative septic complications in IPAA patients should be seriously considered given their detrimental effects on long-term functional outcomes and pouch-retention rates [10,11].

The primary aim of our study was to systematically review literature to evaluate the impact of IFX treatment on early postoperative complications in patients undergoing colectomy and pouch formation (primary IPAA) while receiving biological drugs, and their effect on

complications occurring after ileostomy closure and function. Our secondary aim was to assess the impact of biological drugs on overall complications in patients undergoing any type of surgery for UC.

Materials and Methods

Inclusion criteria

Prospective or retrospective cohort studies comparing postoperative complications were included if they clearly reported on patients undergoing IPAA for UC while receiving IFX with those who did not. Studies mentioning patients with UC, indeterminate colitis and Crohn's disease were evaluated and included only if UC patients were identifiable. Studies were evaluated for potential replication of data. In the case of duplicate publication or similar data from same Institutions, studies were matched and data were merged. Studies were only included if adequate information concerning both treated groups were available. Studies in which the nutritional and general health status and concomitant medications and comorbidities were not reported were excluded from evaluation. Only studies published as full-text article were included. Studies evaluating the effects of other-than-IFX agents were evaluated for inclusion.

Data Search

Available data of all studies published between January 2005 and April 2014 were evaluated for inclusion. The literature searches were carried out on PubMed, Scopus, US National Library of Medicine database (MEDLINE), the Excerpta Medica database (EMBASE), the Cochrane Database of Systematic Reviews. Also Google search engine was searched. Keywords and medical subjects headings (MeSH) used were: "restorative proctocolectomy", "ulcerative colitis", "surgery", "postoperative complications" and "Tumor Necrosis Factor-alpha/antagonists & inhibitors". Free text words were: "inflammatory bowel diseases", "ulcerative colitis complications", "ulcerative colitis", "restorative proctocolectomy", "colectomy", "ileoanal anastomosis", "ileal pouch", "ileal pouch anal

anastomosis", "IPAA", "infliximab", "anti-TNF", "postoperative complications", "perioperative complications", and "function". Limits: publication date between 2005 and 2014. Cross-referencing and related articles were also reviewed. Searches were repeated periodically until April 2014. We excluded experimental articles. Article published in English, French, Spanish, Dutch, or Italian were included.

Outcome measures

Primary outcomes: infectious IPAA-related complications within 30 days after surgery with primary IPAA formation with loop-ileostomy; complications occurring after ileostomy closure and function after IPAA performed while receiving or not biological drugs.

Secondary outcomes: Infectious and noninfectious complications after any type of surgery for UC (subtotal colectomy or IPAA) in patients receiving or not biologics.

Noninfectious complications were defined as: prolonged ileus; thromboembolic complications; cardiovascular, respiratory or renal complications.

Infectious complications were classified as IPAA-related and non-IPAA-related complications. Infectious IPAA-related complications were those directly related to ileoanal anastomosis (i.e. anastomotic leak, pelvic sepsis, abscess, fistula). We included all anastomotic leaks of the IPAA as local infectious complications, even if not classified as such by authors. Infectious non-IPAA-related complications were infectious complications which are not specific of pouch surgery (i.e. pneumonia, urinary tract infection). When assessing the complications of any type of surgery (secondary aim), anastomotic and (colo)rectal stump leaks and SSI were all classified as infectious complications, independently from authors' definition, when possible. Specifically, surgical site infection (SSI) and wound dehiscence were defined according to Centers for Disease Control and Prevention (CDC) criteria [12] and classified as non-IPAA-related infectious complications.

Surgery-definition

The following classification of surgical procedures was adopted.

One-stage procedures: total proctocolectomy with creation of IPAA and no diverting stoma. Two-stage procedures: total proctocolectomy with IPAA and diverting ileostomy, which is closed during the second stage procedure. Three-stage procedures: total abdominal colectomy with end ileostomy, followed by a second stage with completion proctectomy and IPAA either with diverting loop ileostomy, closed during the final third stage, or without a diverting loop-ileostomy (two-stage modified IPAA).

Quality assessment

Each selected article was thoroughly reviewed separately by two authors (FS, GP). Most studies on the topic are observational, retrospective study (e.g. cohort study, case-control study, cross-sectional study). No guidelines exist concerning how to report on such studies, hence we assessed quality with two scores: the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Statement [13], which has a similar aim as the CONSORT Statement, but is designed for observational studies, consisting of a checklist covering 22 items under the headings title and abstract, introduction, methods, results, discussion and other information. Study quality was classified as: high, acceptable, low, and poor according to STROBE. Also, a personal score was used, obtained by the sum of the following variables: number of patients (0 point: <10 patients per group; 1:11-20; 2: >20), study nature (prospective vs retrospective 1 vs 0 points), patient assessment (0: poor; 1: acceptable; 2: good), disease and IPAA assessment (0: poor; 1: acceptable; 2: good; 3: excellent), pouch-related complication assessment (0-1 points), follow-up and outcome description (0-1 points). Article scored below 3 and those classified as “poor” with

STROBE were excluded from evaluation. When available, full-text of articles candidate for being included were collected; for papers published in national-based Journals or without an on-line full-text access, abstracts were collected and reviewed in a similar fashion. Congress proceedings abstracts which were not published as full paper were not included.

Data extraction

Selected publications were read thoroughly and all needed information gathered. Authors were contacted when clarifications were needed. Data of interest were: years and location of studies; year of publication; inclusion/exclusion criteria; perioperative care; postoperative follow-up duration and pathway; number of included patients; patient- and disease-related characteristics; dose and schedule of IFX treatment; concomitant medications (steroids and immunosuppressants); type of surgery; complications (classified as reported above).

Statistical analysis

Continuous variables are expressed as mean ± SD or as median (range). Differences in means between subgroups were compared using *t* test. Comparisons between categorical variables were analysed using the Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results are reported as odds ratio (OR) with 95% confidence interval (CI). A fixed-effect model was used to pool data [14]. Heterogeneity was assessed by means of χ^2 test for heterogeneity and I^2 measure of inconsistency. We calculated the Number Needed to Harm (NNH) as the inverse of the pooled risk differences between groups.

Results

Characteristics of all studies evaluated for inclusion [15-33] after selection are reported in Table 1. Definition and assessment of complications, as well as treated patients are reported in Table 2. Tables are modified from the study of Yang et al. [8]. All reported studies were used for the secondary aims. The characteristics of all studies included for primary aim are reported in Table 3. Systematic study selection flow-chart for analysis is reported in Figure 1.

Study and patient selection and characteristics

For primary aim, only studies clearly reporting on patients diagnosed with UC operated on with IPAA formation and loop-ileostomy (two-stage procedure) were considered for inclusion. These were included if data on patients receiving or not biological drugs were fully available along the text or contacting corresponding authors. The initial search yielded 831 studies. Out of these, 796 did not fit to inclusion criteria. The full-texts of 35 papers were read, and letter to the editors were excluded. Nine papers were identified reporting on patients receiving primary IPAA at the time of first surgery [16,18,19-21,22,24,29,30]. Two papers were excluded at this stage: one because data on patients receiving 3- and 2-stage IPAA were not distinguishable [22]; another one because results were likely to be biased by a significant difference in patients receiving 1-stage IPAA between exposed and non-exposed group (9 vs 35%, p=0.04) [19].

None of these papers was removed after quality assessment. Seven studies reporting on 162 patients receiving biologics and 468 controls all undergoing primary IPAA formation (Table 3) were included for the primary aim meta-analysis. A prevalence of laparoscopic surgery versus open surgery was observed in the patients included in the meta-analysis.

Nineteen studies reporting on any type of surgery in UC patients [15-33] were used for the secondary aims (Table 1, Table 2).

Primary aim: early IPAA-related complications

Potential factors which may have affected results are listed in the footnotes of Table 3 and disclosed for every study (column "notes"). Apart from one study [16] in which exposed patients received more high-dose corticosteroids, no differences were observed among groups in the selected studies. All patients reported by Coquet-Reinier et al.[20] received a laparoscopic IPAA. Figure 2 shows the Forest Plot reporting on the risk of developing IPAA-related complications in patients receiving biologic drugs compared with those who did not. The former were at higher risk of local pelvic complications, OR 4.12 (95%CI 2.37-7.15, I^2=27%), with a NNH of 5.

We conducted subgroup meta-analyses to evaluate the effect on complications of the interval between last biologic administration and of the overall number of administrations.

When considering good quality papers (>4 quality points) reporting a cut-off value of 12 weeks between last administration and IPAA[24,29,30], the risk still seemed higher than controls, but not statistically significant (OR 2.35, 95%CI 0.98-5.64, P=0.06, I^2=0%, three studies) (Figure 3a); conversely, a stronger association with the likeliness of developing IPAA-related complications was observed in patients receiving an average of ≥ 3 administrations in good quality papers (>4 quality points)[18,24,29] (OR 9.59, 95%CI 2.92-31.44, P=0.0002, I^2=0%, three studies) (Figure 3b).

Primary aim: IPAA-related complications after ileostomy closure and function

Three studies[18,24,30] from two large, tertiary US centres compared the complication occurring after ileostomy takedown of patients receiving IPAA being exposed or not to

biologics. Patients receiving biologics at the time of IPAA were at significantly higher risk of developing IPAA-related complications in the long term, OR 2.27 (95%CI 1.27-4.05, I^2=0%). NNH was 4 (Figure 2b).

These studies also reported on pouchitis at 1-year follow-up: patients exposed to biologics showed a trend toward higher prevalence of pouchitis (OR 2.01, CI95% 0.99-4.07), but this finding did not reach statistical significance (Z=1.92, P=0.05) and a moderate heterogeneity was observed among studies (I^2=46%).

Only one study [30] reported on the functional outcomes and quality of life, preventing from further analysis.

Secondary aim: overall complications after any type of surgery

Sixteen studies reporting on 777 patients receiving biologics and 2939 controls undergoing any type of surgery [15-18,20,22-30,32,33] were included. Two-hundred eighty-eight events were observed in the former, compared with 910 in controls. Patients receiving biologics were at slightly higher risk of developing at least one complication, but no statistical differences were observed (P=0.05); studies were moderately heterogeneous (OR 1.19, 95%CI 1.00-1.42, I^2=46%) (Figure 4).

Secondary aim: infectious complications after any type of surgery

Aiming to evaluate all infectious complications (IPAA and non-IPAA related complications) in patients undergoing any type of surgery, we identified fourteen studies reporting on 511 patients receiving biologics and 1386 controls [16-22,25,26,29-33]. Patients receiving biologics were at slightly higher risk of developing infectious complications, however the difference was not significant and studies were moderately heterogeneous (OR=1.12, 95%CI 0.87-1.45, P=0.38, I^2=60%).

The effects of biologic medications on SSI after any type of surgery were separately assessed. Biologics were associated with lower risk of SSI [19,22,25,26,30-33] (OR=0.67, 95%CI 0.45-0.99, P=0.04, I^2=64%, eight studies) (Figure 5a).

Secondary aim: non-infectious complications after any type of surgery

Eleven studies clearly assessed non-infectious complications, reporting on 455 patients receiving biologics and 1077 controls [16-18,20,22,25,26,29,30,32,33]. Complications were higher in controls, but difference was not significant (OR= 0.97, 95%CI 0.75-1.27, P=0.85, I^2=31%).

Discussion

Our meta-analysis focussed on the risk of postoperative complications in patients undergoing primary IPAA formation who received biologics, and included studies obtaining at least 3/10 quality evaluation score and STROBE classification > poor (Table 3). We found a significant increased risk of IPAA-related complications in the short term (OR 4.57, 95%CI 2.73-7.66), suggesting that these may affect one out of five patients undergoing surgery in these settings (NNH= 5). When analyzing the effects of preoperative biologics on pouch health after ileostomy closure in patients receiving primary IPAA, we observed a significant higher risk of IPAA-related complications (OR 2.27, 95%CI 1.27-4.05), potentially affecting 25% of these patients (NNH=4). Moreover, we observed a trend toward higher risk of pouchitis at 1-year follow-up in the biologic group (OR 2.01, CI95% 0.99-4.07, Z=1.92, P=0.05). Interestingly, no significant increased risks of overall[15-18,20,22-30,32,33], infectious [16-22,25,26,29-33] or non-infectious complications [16-18,20,22,25,26,29,30,32,33] were found when including into analysis patients undergoing any type of surgery. This is likely to be due to heterogeneity among study populations and interventions.

Agreement exists about the usefulness and efficacy of biological drugs in patients suffering from inflammatory bowel diseases. UC patients are being treated with biologics since almost 10 years[1]. Up to 30% of UC patients may need surgery during their life, IPAA being the treatment of choice at any age[3,5,6,24,34,35], removing the entire diseased colon and abolishing the risk of developing malignancies [36,37]. IFX has shown efficacy in postponing surgery in patients presenting acutely, but the rate of colectomy in the long-term has been shown to be similar to that of patients treated before the introduction of biological drugs [2,3]. However, biologics may be associated with serious

adverse effects, e.g. increased incidence of infections. This may affect the perioperative and postoperative course and management of patients who often undergo surgery in poor general health status.

This concern has been much debated recently, and studies have been reported concerning the effect of biologics on patients undergoing surgery for UC [2,7-10,15-33,38]. The vast majority of these papers is retrospective and reports on a very limited number of patients, justifying the contrasting results observed. No prospective specific studies are available in the literature concerning the risk of perioperative and postoperative complications in UC patients operated on while receiving biological drugs.

Several recently published meta-analyses investigating the effects of biological drugs on the postoperative complication rate in UC patients have not clarified their real impact[2,7-9]. This is due to many factors affecting the reproducibility of the findings. First, confusion exists among available studies about the type of surgery performed in UC patients operated on, as they lack a homogeneous definition of the procedure. We reported above this definition to avoid confusion. The assessment of the overall and IPAA-related complications is often suboptimal. Also, studies include patients undergoing elective and emergency surgery, with or without primary IPAA formation, and with or without a diverting stoma at the time of IPAA. For our primary aim we only sought for IPAA-related complications affecting patients receiving surgery with primary IPAA formation under the effects of biological drugs, to avoid misleading results. Second, another factor to take into account is the presence of multiple confounders, mainly represented by concomitant medications and patient-related variables. According to recent reports on this topic [39], we identified factors which may be independently predicting peri- and postoperative complications (body mass index, concomitant high dose steroids, nutritional status, blood-transfusions, colitis extent, and co-morbidities, operating surgeon), we posed it into

perspective and looked for significant differences among included studies population (Table 3). Patients of all but one[16] of these studies were homogeneous in each cohort, making results reliable. Third, the number of biological administrations and the interval between last administration and surgery are not always clearly stated. Finally, great variability is observed when analysing the definitions of perioperative complications (Table 2).

Concerning the time interval between the last biologic administration, most studies agree that 12 weeks is the ideal cut-off point for IFX due to drug clearance [40] and disappearance of anti-IFX antibodies at 12 weeks [41], but some [24] suggested that a lower threshold could be chosen as pharmacokinetic studies in UC patients showed a 14 days half-life at the longest [40-42]. The half-life of other included biologics was considered in each study for establishing the cut-off value (i.e. 4 weeks for adalimumab[30]). We performed a sub-group analysis of IPAA-related complications including only good quality studies studies on patients clearly receiving primary IPAA within 12 weeks from the last IFX effusion[24,29,30], and found that the risk difference was not statistically significant (OR 2.35, 95%CI 0.98-5.64, P=0.06, I^2=0%, three studies). On the contrary, the risk of developing IPAA-related complications was significantly associated with the number of administrations received (at least 3) [18,24,29] (OR 9.59, 95%CI 2.92-31.44, P=0.0002, I^2=0%, three studies). These findings confirm the observations of some authors that IFX can have an effect on postoperative complications even in patients receiving the last infusion over 2-3 months before surgery [16,18], suggesting that the cumulative dose of the drug may be more important the time-interval alone. Biologics may affect postoperative morbidity in the short-term as necrosis factor is part of a complex proinflammatory mechanism [18,28]. This should be posed into perspective when dealing with patients who received the last effusion over 12 weeks before surgery. Also, given that

we included only primary IPAA patients and that patients receiving more than 2 IFX effusions are those likely to have had a response to drug – avoiding emergency colectomy – one could argue that our data further reduced the risk of including into analysis sick patients with predictable worse outcomes.

As clearly showed in Table 2, the definitions of infectious and noninfectious complications vary significantly among studies. For this reason, we classified complications independently from authors' definition (see Outcome Measures). The discrepancies in the classification are relevant, as these can influence the results of the analysis. Yang et al. [8] recently reported in their meta-analysis on UC patients undergoing any type of abdominal surgery that preoperative IFX within 12 weeks was not associated with overall and noninfectious complications, and that it had a protective effect against infectious postoperative complications (OR=0.43, 95%CI 0.22-0.83, P=0.01). Interestingly, the same authors conducted a meta-analysis of the same subject in 2010[7] and concluded that preoperative IFX increased the risk of post-operative complications. When considering patients undergoing any type of surgery our results were not dissimilar from that of Yang[8] concerning overall and noninfectious complications, conversely we found a trend toward higher infectious complications with preoperative biologics though not statistically significant. However, when analyzing only SSI, we observed that IFX reduced the risk of this infectious complication (OR=0.67, 95%CI 0.45-0.99, P=0.04, I^2=64%, eight studies[19,22,25,26,30-33]). This may account for an inclusion bias of the infectious complications outcome in the paper by Yang et al.[8], further suggested by the observation that heterogeneity of the studies included in our analysis is dramatically reduced and significance of the protective effect over SSI is increased by removing a paper[30] that had not been published at time of their analysis (OR 0.28, 95%CI 0.15-0.53, P < 0.0001, I^2=0%, seven studies [19,22,25,26,31-33]) (Figure 5b). It is clear that inflammatory bowel

diseases are a risk factor for SSI[43] which may require measures to prevent postoperative complications[44], suggesting that the potential effects of IFX on wound healing and SSI are interesting and need to be further investigated, as only in vitro and animal studies are available, with equivocal results[45,46]. At the same time, our observation highlights the importance of clearly defining and identifying events and outcomes when analyzing data.

A factor making interpretation of previous meta-analyses difficult is the inclusion of studies which, though of high quality, report on UC patients undergoing a variety of abdominal surgical procedures. In our analysis, when selecting patients receiving IPAA formation, IFX was significantly associated with higher risk of developing early as well as post-ileostomy closure IPAA-related complications. This has a practical implication. Sick patients, those receiving high-dose steroids, and those with severe colitis obviously need a three-stage procedure. Our aim was to propose a decision-making strategy in patients undergoing planned or elective surgery for UC while on treatment with biologics. Even if data on functional results in the long-term were not evaluable, it is known that early septic after IPAA can have a detrimental effect on pouch function and survival[10,11]. Hence we would suggest a prudent approach to patients who have received more than two effusions, even in good health status, avoiding primary pouch construction. A three-stage or a three-stage modified procedure would be safe options.

Our meta-analysis shares some of the above reported limitations with other meta-analyses in the field [2,7-9]. Unmodifiable confounders were the retrospective design of the high-quality included studies and the inclusion of patients receiving other-than-IFX biological drugs. We tried to reduce the effects of the other bias-generating variables.

Conclusions

Despite all reported limitations, this is the first meta-analysis to evaluate the effects of preoperative anti-TNF treatment on postoperative IPAA-related complications after primary IPAA formation for UC. When considering patients undergoing any type of abdominal procedure for UC, preoperative use of biologics did not seem to be associated with significant increase of postoperative complications, suggesting that the influence of important confounding factors can hardly be removed. However, early pouch-specific complications and complications occurring after ileostomy closure were significantly higher in patients undergoing IPAA with primary pouch formation receiving IFX. This can be attributed to adverse effect by biologics themselves, but a correlation between recent biological therapy and complications - possibly due to a more severe disease (e.g. clinically masked by a partial response of the antibodies) rather than an effect of the biologics themselves - cannot be ruled out, at least in some patients. In any event, we would suggest delaying pouch construction in patients who have received biologics. The effects of dose and the optimal interval between the last effusion and surgery need to be further elucidated.

There is the need of prospective, large trials considering confounders related to patients, disease and surgical procedure performed to obtain definitive results.

Legends to Figures

Figure 1. Flow-chart of study selection for inclusion in the analysis

Figure 2. A. Forest plot of the outcomes (early IPAA-related postoperative complication) of patients undergoing IPAA with (IFX) or without (control) previous exposure to biologics. Patients who received previous biologic treatment had an OR 4.12 (95%CI 2.37-7.15), with a number needed to harm (NNH) of 5 of developing early IPAA-related complications than those who did not (Mantel-Haenszel fixed effect). P<0.0001. Heterogeneity is low: I^2=27%. IFX: infliximab

B. Forest plot of the outcomes (post-ileostomy closure IPAA-related complication) of patients undergoing IPAA with (IFX) or without (control) previous exposure to biologics. Patients who received previous biologic treatment had an OR 2.27 (95%CI 1.27-4.05), with a number needed to harm (NNH) of 4 of developing late IPAA-related complications than those who did not (Mantel-Haenszel fixed effect). No heterogeneity is observed: I^2=0%. IFX: infliximab

Figure 3. A. Forest plot of a subgroup meta-analyses of the outcomes (early IPAA-related postoperative complication) of patients undergoing IPAA with biologics received within 12 weeks from IPAA formation or without (control) previous exposure to biologics. Only studies with good quality score (> 4) are included[22,27,28]. Patients who received previous biologic treatment had an OR 2.35 (95%CI 0.98-5.64,), without statistical significance (P=0.06) (Mantel-Haenszel fixed effect). No heterogeneity is observed: I^2=0% IFX: infliximab.

B. Forest plot of a subgroup meta-analyses of the outcomes (early IPAA-related postoperative complication) of patients undergoing IPAA after 3 or more biologics administrations or without (control) previous exposure to biologics. Only studies with good quality score (> 4) are included[16,22,27]. Patients who received previous biologic treatment had an OR 9.59 (95%CI 2.92-31.44) P=0.0002 (Mantel-Haenszel fixed effect). No heterogeneity is observed: I^2=0%. IFX: infliximab.

Figure 4. Forest plot of the outcomes (total early postoperative complication) of patients undergoing any type of surgery with (IFX) or without (control) previous exposure to biologics. Patients who received previous biologic treatment had an OR 1.19 (95%CI 1.00-1.42) of developing early postoperative complications than those who did not, P=0.05 (Mantel-Haenszel fixed effect). Heterogeneity is moderate: I^2=46%. IFX: infliximab

Figure 5. A. Forest plot of the surgical site infection (SSI) of patients undergoing any type of surgery with (IFX) or without (control) previous exposure to biologics. Patients who received previous biologic treatment had an OR 0.67 (95%CI 0.45-0.99) of developing SSI than those who did not, P=0.04 (Mantel-Haenszel fixed effect). Heterogeneity is moderate: I^2=64%. IFX: infliximab.

B. Forest plot of the surgical site infection (SSI) of patients undergoing any type of surgery with (IFX) or without (control) previous exposure to biologics after removing the paper by Gu et al.[28] Patients who received previous biologic treatment had an OR 0.28 (95%CI 0.15-0.53) of developing SSI than those who did not, P<0.0001 (Mantel-Haenszel fixed effect). No heterogeneity is observed: I^2=0%. IFX: infliximab

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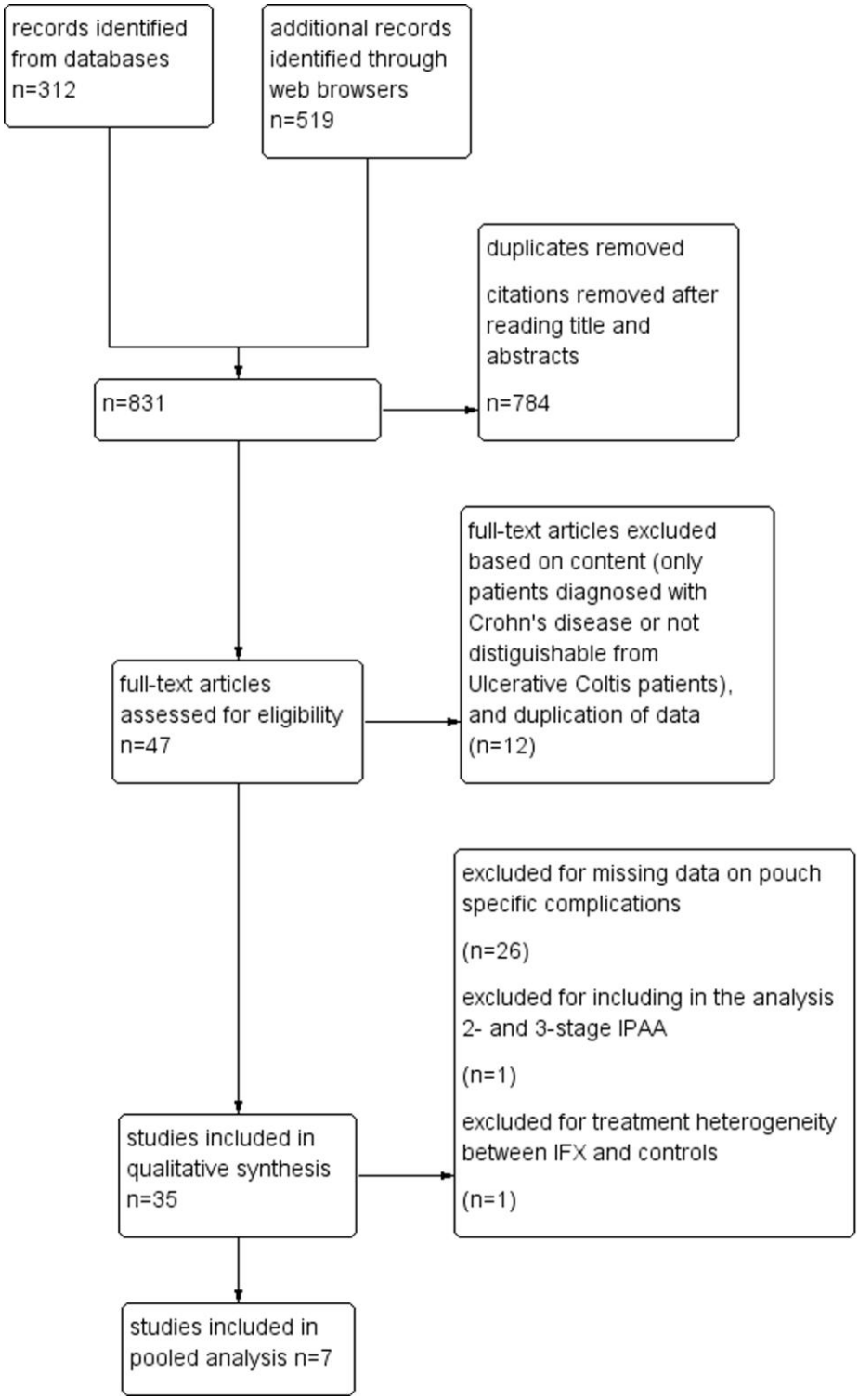
Figure 1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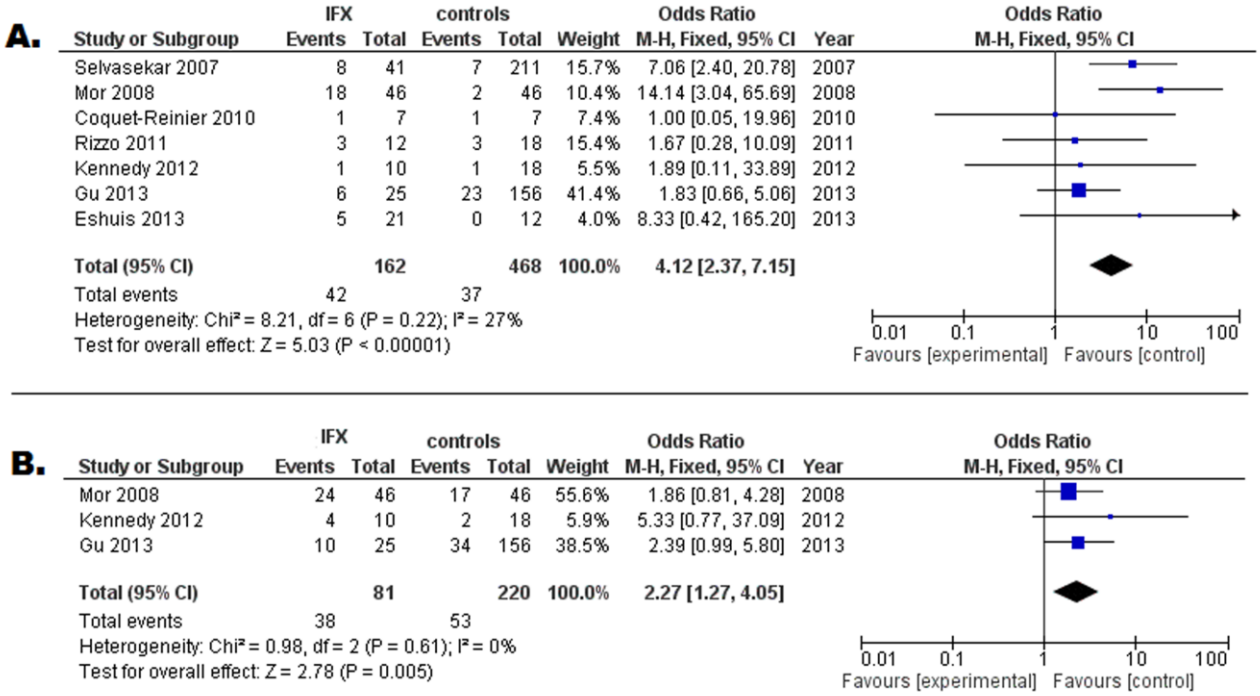
full-text articles assessed for eligibility n=47
excluded for missing data on pouch specific complications
(n=26)
excluded for including in the analysis 2- and 3-stage IPAA
(n=1)
excluded for treatment heterogeneity between IFX and controls
(n=1)
studies included in qualitative synthesis n=35
studies included in pooled analysis n=7

Figure 2


A.
IFX
controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Selvasekar 2007 8 41 7 211 15.7% 7.06 [2.40, 20.78] 2007
Mor 2008 18 46 2 46 10.4% 14.14 [3.04, 65.69] 2008
Coquet-Reinier 2010 1 7 1 7 7.4% 1.00 [0.05, 19.96] 2010
Rizzo 2011 3 12 3 18 15.4% 1.67 [0.28, 10.09] 2011
Kennedy 2012 1 10 1 18 5.5% 1.89 [0.11, 33.89] 2012
Gu 2013 6 25 23 156 41.4% 1.83 [0.66, 5.06] 2013
Eshuis 2013 5 21 0 12 4.0% 8.33 [0.42, 165.20] 2013
Total (95% CI) 162 468 100.0% 4.12 [2.37, 7.15]
Total events 42 37
Heterogeneity: Chi² = 8.21, df = 6 (P = 0.22); I² = 27%
Test for overall effect: Z = 5.03 (P < 0.00001)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

B.
IFX
controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Mor 2008 24 46 17 46 55.6% 1.86 [0.81, 4.28] 2008
Kennedy 2012 4 10 2 18 5.9% 5.33 [0.77, 37.09] 2012
Gu 2013 10 25 34 156 38.5% 2.39 [0.99, 5.80] 2013
Total (95% CI) 81 220 100.0% 2.27 [1.27, 4.05]
Total events 38 53
Heterogeneity: Chi² = 0.98, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Figure 3

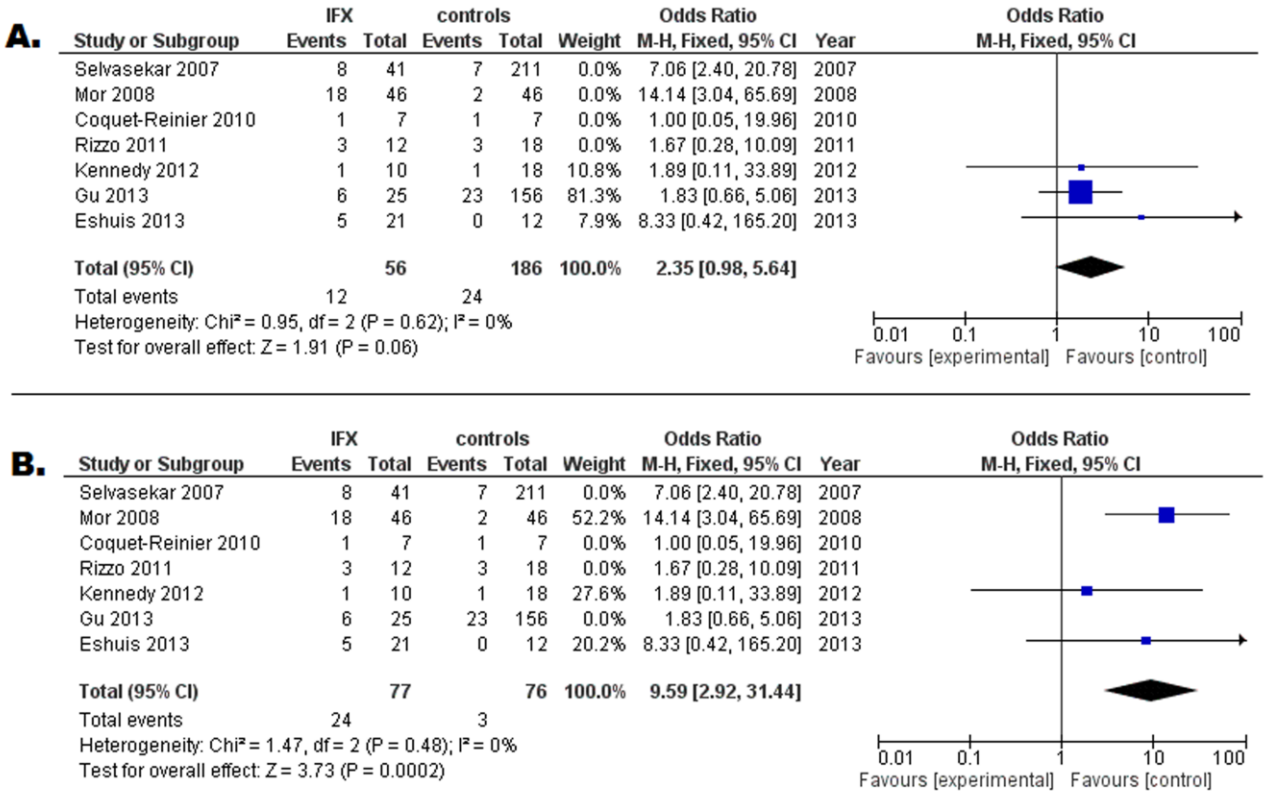

A.
IFX
controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Selvasekar 2007 8 41 7 211 0.0% 7.06 [2.40, 20.78] 2007
Mor 2008 18 46 2 46 0.0% 14.14 [3.04, 65.69] 2008
Coquet-Reinier 2010 1 7 1 7 0.0% 1.00 [0.05, 19.96] 2010
Rizzo 2011 3 12 3 18 0.0% 1.67 [0.28, 10.09] 2011
Kennedy 2012 1 10 1 18 10.8% 1.89 [0.11, 33.89] 2012
Gu 2013 6 25 23 156 81.3% 1.83 [0.66, 5.06] 2013
Eshuis 2013 5 21 0 12 7.9% 8.33 [0.42, 165.20] 2013
Total (95% CI) 56 186 100.0% 2.35 [0.98, 5.64]
Total events 12 24
Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]
B.
IFX
controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Selvasekar 2007 8 41 7 211 0.0% 7.06 [2.40, 20.78] 2007
Mor 2008 18 46 2 46 52.2% 14.14 [3.04, 65.69] 2008
Coquet-Reinier 2010 1 7 1 7 0.0% 1.00 [0.05, 19.96] 2010
Rizzo 2011 3 12 3 18 0.0% 1.67 [0.28, 10.09] 2011
Kennedy 2012 1 10 1 18 27.6% 1.89 [0.11, 33.89] 2012
Gu 2013 6 25 23 156 0.0% 1.83 [0.66, 5.06] 2013
Eshuis 2013 5 21 0 12 20.2% 8.33 [0.42, 165.20] 2013
Total (95% CI) 77 76 100.0% 9.59 [2.92, 31.44]
Total events 24 3
Heterogeneity: Chi² = 1.47, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Figure 4

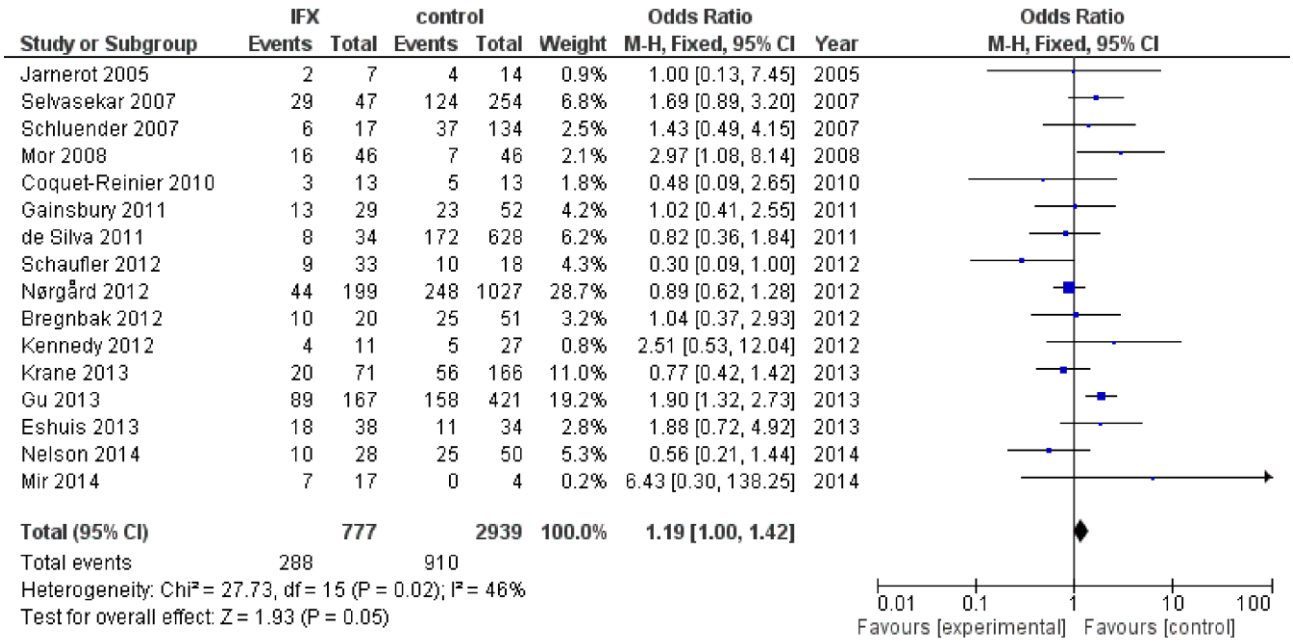
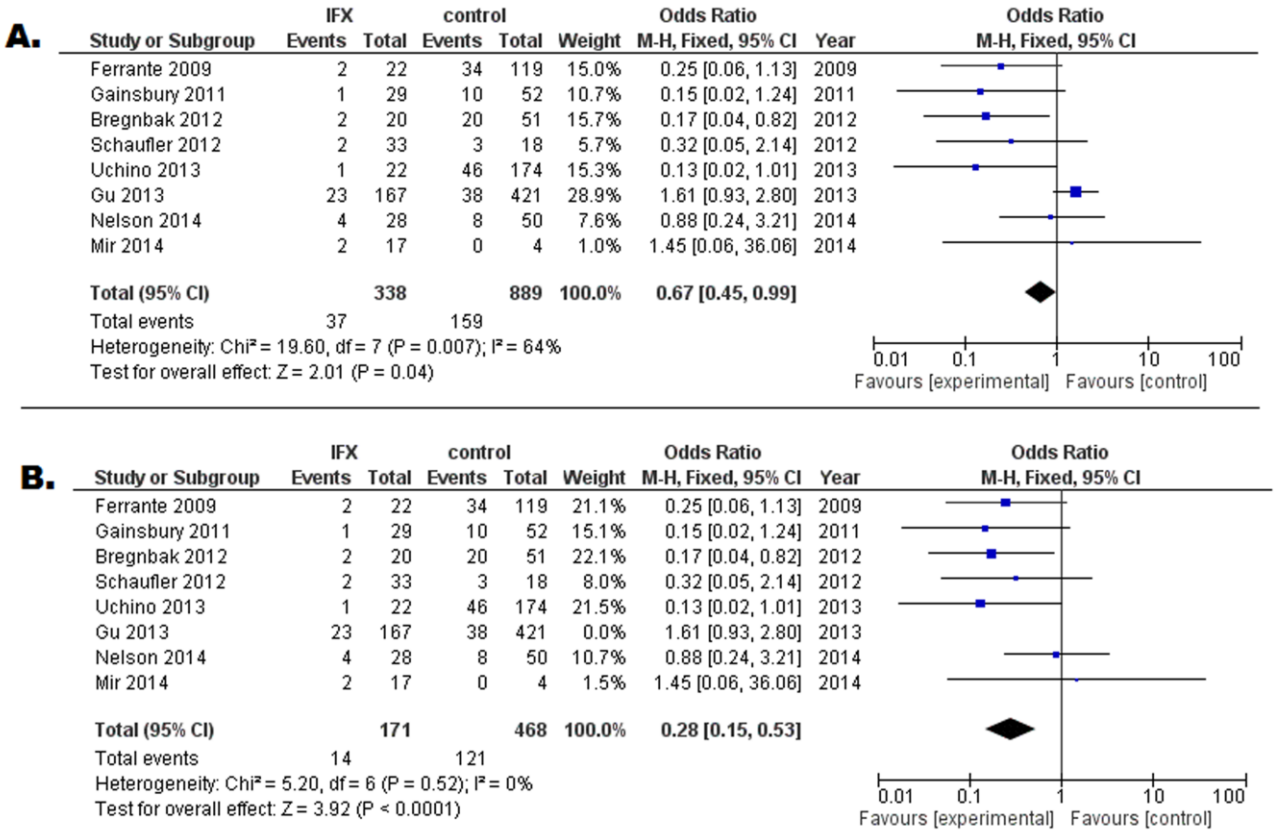

IFX
control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Jarnerot 2005 2 7 4 14 0.9% 1.00 [0.13, 7.45] 2005
Selvasekar 2007 29 47 124 254 6.8% 1.69 [0.89, 3.20] 2007
Schluender 2007 6 17 37 134 2.5% 1.43 [0.49, 4.15] 2007
Mor 2008 16 46 7 46 2.1% 2.97 [1.08, 8.14] 2008
Coquet-Reinier 2010 3 13 5 13 1.8% 0.48 [0.09, 2.65] 2010
Gainsbury 2011 13 29 23 52 4.2% 1.02 [0.41, 2.55] 2011
de Silva 2011 8 34 172 628 6.2% 0.82 [0.36, 1.84] 2011
Schaufler 2012 9 33 10 18 4.3% 0.30 [0.09, 1.00] 2012
Nørgård 2012 44 199 248 1027 28.7% 0.89 [0.62, 1.28] 2012
Bregnbak 2012 10 20 25 51 3.2% 1.04 [0.37, 2.93] 2012
Kennedy 2012 4 11 5 27 0.8% 2.51 [0.53, 12.04] 2012
Krane 2013 20 71 56 166 11.0% 0.77 [0.42, 1.42] 2013
Gu 2013 89 167 158 421 19.2% 1.90 [1.32, 2.73] 2013
Eshuis 2013 18 38 11 34 2.8% 1.88 [0.72, 4.92] 2013
Nelson 2014 10 28 25 50 5.3% 0.56 [0.21, 1.44] 2014
Mir 2014 7 17 0 4 0.2% 6.43 [0.30, 138.25] 2014
Total (95% CI) 777 2939 100.0% 1.19 [1.00, 1.42]
Total events 288 910
Heterogeneity: Chi² = 27.73, df = 15 (P = 0.02); I² = 46%
Test for overall effect: Z = 1.93 (P = 0.05)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Figure 5


A.
IFX
control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Ferrante 2009 2 22 34 119 15.0% 0.25 [0.06, 1.13] 2009
Gainsbury 2011 1 29 10 52 10.7% 0.15 [0.02, 1.24] 2011
Bregnbak 2012 2 20 20 51 15.7% 0.17 [0.04, 0.82] 2012
Schaufler 2012 2 33 3 18 5.7% 0.32 [0.05, 2.14] 2012
Uchino 2013 1 22 46 174 15.3% 0.13 [0.02, 1.01] 2013
Gu 2013 23 167 38 421 28.9% 1.61 [0.93, 2.80] 2013
Nelson 2014 4 28 8 50 7.6% 0.88 [0.24, 3.21] 2014
Mir 2014 2 17 0 4 1.0% 1.45 [0.06, 36.06] 2014
Total (95% CI) 338 889 100.0% 0.67 [0.45, 0.99]
Total events 37 159
Heterogeneity: Chi² = 19.60, df = 7 (P = 0.007); I² = 64%
Test for overall effect: Z = 2.01 (P = 0.04)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]

B.
IFX
control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year
M-H, Fixed, 95% CI
Ferrante 2009 2 22 34 119 21.1% 0.25 [0.06, 1.13] 2009
Gainsbury 2011 1 29 10 52 15.1% 0.15 [0.02, 1.24] 2011
Bregnbak 2012 2 20 20 51 22.1% 0.17 [0.04, 0.82] 2012
Schaufler 2012 2 33 3 18 8.0% 0.32 [0.05, 2.14] 2012
Uchino 2013 1 22 46 174 21.5% 0.13 [0.02, 1.01] 2013
Gu 2013 23 167 38 421 0.0% 1.61 [0.93, 2.80] 2013
Nelson 2014 4 28 8 50 10.7% 0.88 [0.24, 3.21] 2014
Mir 2014 2 17 0 4 1.5% 1.45 [0.06, 36.06] 2014
Total (95% CI) 171 468 100.0% 0.28 [0.15, 0.53]
Total events 14 121
Heterogeneity: Chi² = 5.20, df = 6 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.92 (P < 0.0001)
0.01 0.1 1 10 100
Favours [experimental] Favours [control]