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# Effects of Successive Switches to Different Biosimilars Infliximab on Immunogenicity in Chronic Inflammatory Diseases in Daily Clinical Practice

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## **ABSTRACT**

**Objective:** To evaluate the risk of immunogenicity in patients with chronic inflammatory diseases who experienced successive non-medical switches to different biosimilars infliximab.

**Patients and Methods:** Observational study over a 3-year observation period assessing the risk of immunogenicity in i) patients in maintenance therapy with innovator infliximab who were successively switched to CT-P13, then to SB2 (cohort-1) and ii) biologic-naive patients initiated with CT-P13 before being switched to SB2 (cohort-2). A proportion meta-analysis was also performed, integrating our results to 16 additional studies.

**Results:** Cohort-1 included 265 patients who switched to CT-P13, and 140 patients were subsequently switched to SB2. Among the 235 anti-drug antibody (ADA)-free patients at baseline, 20 patients (8.5%) developed ADA over the 3-year observation period (rate of 3 for 100 patient years). Cohort-2 included 44 patients, of whom 29 subsequently switched to SB2. A total of 11 patients (25%) developed ADA within 3 years (rate of 14 for 100 patients years). We found no influence of the number of biosimilars infliximab received on ADA development in both cohorts. The risk of treatment discontinuation was significantly higher in patients with positive ADA in both cohorts. The meta-analysis including our data exposed an incidence of immunogenicity of 4.7% (95% CI 3.5-6.1%) after the switch from innovator infliximab to biosimilar infliximab and 21.1% (95% CI 13.1-30.3%) in patients initiating biosimilar infliximab.

**Conclusion:** Immunogenicity was not favored by successive non-medical switches to biosimilars infliximab in our study, but was associated with treatment discontinuation.

The use of targeted biological treatments has transformed the entire management of chronic inflammatory disorders. Since a few years, the expiration of their patents had led to the development of biosimilar products, allowing a reduction of health expenditure. Biosimilars being complex molecules, their development need strict comparability study.[1] Regarding Infliximab, the first biosimilar CT-P13 entered the market in Europe in 2013 and United States in 2016, with the same indications than the innovator. Biosimilarity between CT-P13 and its innovator has been demonstrated by non-clinical and clinical studies including two pivotal clinical studies (PLANETRA and PLANETAS).[2-3] In addition, systematic non-medical switch from innovator Infliximab to its biosimilar CT-P13 in inflammatory chronic diseases in real clinical practice setting was associated with no significant changes in objective clinical parameters.[4,5] Then, other biosimilars have been approved, such as SB2 in 2017.[6]

Currently, immunogenicity constitutes one important concern about these therapies. Indeed, it is known that the presence of anti-drug antibodies (ADA) is associated with a decrease of trough-serum drug levels, lower clinical response and more side effects.[3, 7] Infliximab is one of the most immunogenic anti-tumor necrosis factor (anti-TNF)- $\alpha$  therapies; thus the prevention of the immunization and the clinical management of its consequences is a key clinical issue.[8] According to previous clinical studies, ADA directed against innovator Infliximab recognize and bind CT-P13, illustrating that these two treatments may have common immunodominant epitopes.[9] For this reason, it is necessary to ensure that switch to biosimilar is not associated with increased risk of immunisation. Although previous studies were reassuring, they did not evaluate successive switches in the same patient and follow-up period was limited.

Therefore, the main objective of this study was to evaluate in a usual care setting the risk and factors influencing immunogenicity i) in patients who experienced successive non-medical

switches from innovator infliximab to a first then a second biosimilar infliximab, and ii) in patients who switched from a first to a second biosimilar infliximab. Another objective of this study was to integrate these results to previous published data through a comprehensive meta-analysis following a systematic literature research.

## **METHODS**

**Study design:** A prospective observational usual care study was conducted in Rheumatology, Gastroenterology and Internal Medicine departments of Cochin Hospital.

**Study population:** Two independent cohorts were constituted; the first cohort, named cohort-1, included patients who were on maintenance therapy with the original treatment before the successive non-medical switches to biosimilars.[4] The second cohort, named cohort-2, included biologic-naive patients who received a first infliximab biosimilar before being non-medically switched to a second.

**Inclusion criteria:** All patients followed-up in Cochin Hospital, on maintenance therapy with innovator infliximab, and considered controlled for their disease according to their treating physician, were systematically screened for inclusion in cohort-1. Adult patients who agreed to switch to CTP-13, and who had received at least 3 infusions of innovator infliximab prior to the switch, were eligible for inclusion in this cohort.[4] Adult patients, naive of infliximab, who initiated CT-P13 and agreed to participate to the study were eligible for inclusion in cohort-2.

All included patients agreed to participate in the study after receiving informed consent, which was recorded in the medical source file. The protocol and the informed consent document have received Institutional Review Board/Independent Ethics Committee

(IRB/IEC) approval before initiation of the study (“Comité de Protection des Personnes”, Paris Ile de France I).

**Setting:** Patients from cohort-1 were switched at inclusion visit to biosimilar infliximab CT-P13 at the same dose and frequency as innovator infliximab, between October and December 2015. Then, the second switch from CT-P13 to the second biosimilar infliximab SB2 started in December 2017 (minimum exposure time on CT-P13 before the second switch to SB2: 23 months). Patients were then evaluated at each infusion visit until the end of the observation period in December 2018.

Patients from cohort-2 received their first infusion of bisimilar infliximab CT-P13 between November 2015 and October 2017. The switch to the second biosimilar infliximab SB2 occurred in December 2017 (minimum exposure on CT-P13 time before the switch to SB2: 2 months) and patients were evaluated at each infusion visit until December 2018.

**Clinical and laboratory data:** Data were collected at each patient visit through a face-to-face interview and with the validation from the medical file in a standardized case-report form that included: diagnoses; demographic parameters (age, gender, disease duration, body mass index, BMI) ; current and past medication use (including concomitant treatment with methotrexate), duration of treatment with innovator infliximab, number of infusions and dose of the last infusion.

Infliximab trough levels and anti-drug antibodies (ADA) were assessed in the morning prior to each infusion using a validated enzyme-linked immune-absorbent assay (ELISA, LISA-TRACKER Duo Infliximab, Theradiag, Croissy-Beaubourg, France). This kit which has been validated for the detection of ADA and the measurement of infliximab trough levels in patients treated with innovator and biosimilar infliximab. The Intra-assay coefficient of

variation ranged from 4.1% to 8.5% for the detection of ADA and from 3.9% to 11% for the measurement of infliximab trough levels. The Inter-assay coefficient of variation ranged from 10.2% to 15.8% for the detection of ADA and from 8.2% to 17.3% for the measurement of infliximab trough levels. Immunogenicity was defined by the detection of positive anti-drug antibodies (ADA  $\geq$ 10 ng/mL), at least at two consecutive time points.

**Primary Outcome of the study:** The primary outcome of the study was the development of immunogenicity during the observation period.

**Secondary outcomes:** Secondary outcomes were i) the point prevalence of positive ADA at baseline visit in cohort-1, ii) the influence of the successive switches to biosimilars on the risk of immunogenicity in both cohorts, iii) factors associated with ADA generation in both cohorts, iv) the impact of ADA positivity on treatment discontinuation and v) the retention rate of biosimilar infliximab at the end of the observation period in both cohorts.

**Statistical analysis:** All data are expressed as mean values  $\pm$  standard deviation (SD) or number and percentage (%) for continuous and categorical variables, accordingly. Statistical analysis was performed using Medcalc (v18.9.1). To seek for associations between the presence of ADA and potential risk factors of immunization at baseline in cohort 1, we used the unpaired t-test for two-group comparisons (continuous variables) and the chi-square test for differences in frequency (binary variables). Retention rate of biosimilar infliximab was estimated by Kaplan-Meier survival curves. To identify predictive factors of ADA generation in cohorts 1 and 2, we used cox proportional-hazard regression.

### **Systematic literature research and meta-analysis:**

Eligible studies were studies reporting the incidence of ADA occurrence in patients who switched from innovator to a biosimilar infliximab or who were initiated with a biosimilar infliximab. We included observational studies, for whom The Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines were followed and randomized controlled trials (RCTs).[10] We searched MEDLINE and Embase databases between January 1960 and April 2019 using the terms (biosimilar OR infliximab OR CT-P13 OR SB2) AND (immunogenicity OR anti-drug antibodies). The Medical subject heading (MeSH) terms were used for all databases, and a keyword search was substituted when the MeSH search was not available. All MeSH search terms were exploded. In addition, reference lists of the papers initially detected were searched by hand to identify additional relevant reports. No language restriction was applied. Eligibility of references retrieved by the search was assessed independently by two of the authors (A.L. and J.A.) and disagreements resolved at each step. We selected studies that reported sufficient data to calculate the incidence of ADA seroconversion. Data were extracted from the selected studies using a predefined standardized form.

Quality assessment of individual observational studies was performed using the Newcastle–Ottawa Scale. This scale, specific for cohort or case-control studies, uses a star rating system (range: 0–9 stars) scoring three aspects of the study: selection of groups, comparability and ascertainment of the outcome of interest. The quality of RCTs was evaluated with the Jadad scale.[11] It contains two questions for randomization and masking and one question evaluating the reporting of withdrawals and dropouts. Each question entails a yes or no response option. In total, five points can be awarded, with higher scores indicating superior quality.

We calculated in each study a proportion based on the number of patients with positive ADA among the total number of patients. Each individual prevalence was first transformed into a

quantity via the Freeman-Tukey variance-stabilizing transformation. A weighted mean of the transformed proportions was calculated, using a DerSimonian-Laird random effects model. The combined prevalence was calculated as the back-transform of this weighted mean.[12,13] Statistical heterogeneity was tested by Q-test ( $\chi^2$ ). This test allows description of the percentage of total variation across trials that is attributable to statistical heterogeneity rather than chance. I<sup>2</sup>-values of 25, 50 and 75% correspond to low, moderate and high between-trial heterogeneity of results, respectively.[14-15] Fixed and random-effects models based on Q-statistics for heterogeneity were used for homogeneous and heterogeneous trials, respectively. MedCalc software Medcalc (v18.9.1) was used for all these analyses.

## RESULTS

### Study population

Cohort-1 was constituted of 265 patients on maintenance therapy with innovator infliximab who systematically switched to a first biosimilar infliximab (CT-P13) (**Table 1**): 135 patients had axial spondyloarthritis (axSpA) (51%), 64 inflammatory bowel diseases (IBD) (24%), 31 rheumatoid arthritis (RA), 22 psoriatic arthritis (PsA) (8%), 8 uveitis (3%) and 5 other chronic inflammatory diseases (3 vasculitis and 2 AA amyloidosis) (2%). Among these 265 patients, 140 patients switched to the second biosimilar infliximab (SB2), starting from December 2017 (including 72 patients with axSPA, 38 with IBD and 15 with RA) (**Table 2**), 26 remained treated with CT-P13, and innovator infliximab was re-established in 55 patients, mainly due to experienced inefficacy of CT-P13 (47/55, 85%) (**Figure 1A**). Of note, innovator infliximab was re-established in 19 patients after the first biosimilar infusion, 14 after the second infusion, 17 after the third infusion and 5 after >3 infusions.

A total of 60 patients experienced treatment discontinuation during the observation period. At the time of treatment discontinuation, 39 patients were receiving CT-P13, 8 SB2 following CT-P13, and 13 innovator infliximab. Discontinuation was related to primary or secondary loss of efficacy (n=26), side effects (n=20, including 4 infusion-related reactions), diagnosis of neoplasia (n=6), sustained remission (n=6), and death (n=2).

Cohort-2 consisted of 44 patients naive of infliximab who initiated a treatment with CT-P13: 20 with AxSpA (45.5%), 9 with IBD (20.5%), 9 with RA (20.5%), 4 with PsA (9%) and 2 with other chronic inflammatory diseases (one patient with Behcet disease and one with undifferentiated arthritis) (4.5%) (**Table 1**). Among these patients, 29 switched to SB2 (including 11 with AXSpA, 8 with IBD and 7 with RA) (**Table 2**), 5 remained treated with CT-P13 and 10 discontinued the treatment before the switch to SB2 (**Figure 1B**). A total of 15 patients experienced treatment discontinuation during the observation period, including 5 patients who have interrupted their treatment after the switch. Causes of discontinuation were primary or secondary lack of efficacy (10 patients), occurrence of side effects (n=4, including 2 infusion-related reactions) and diagnosis of lymphoma in a single patient.

## **Analysis of the primary outcome**

### **Cohort-1**

Among the 235 ADA negative patients at baseline, 20 patients developed ADA during the 3-year observation period (8.5%), corresponding to a rate of 3 for 100 patient years. All patients with positive ADA had undetectable infliximab trough levels (<0.30 µg/mL). ADA titers ranged from 10 to >200 ng/mL, and 15/20 patients had titers >200 ng/mL.

The incidence of ADA development was 11% in AxSpA (13/120 patients), 3.5% in IBD (2/57 patients), 8% in RA (2/25 patients) and 10% in PsA (2/20 patients). Positive ADA were detected in 10 patients during exposition to CT-P13 and 6 during exposition to SB2. Four

patients were back to innovator INF at the time of ADA seroconversion. The mean time to ADA seroconversion was  $22\pm 13$  months (range: 1-36 months). The majority of patients who developed ADA during the observation period (16/20, 80%) had received innovator infliximab for more than 24 months prior to the switch (**Table S1**).

### **Cohort-2**

In infliximab-naïve patients, 11/44 (25%) patients developed ADA during the observation period, corresponding to a rate of 14 for 100 patients years. All patients with positive ADA had undetectable infliximab trough levels ( $<0.30$   $\mu\text{g/mL}$ ). The incidence of ADA development was 20% in AxSpA (4/20 patients), 22% in IBD (2/9 patients), 44% in RA (4/9 patients) and 25% in PsA (1/4 patients). The mean time to positive ADA detection was  $13\pm 11$  months (range: 1-31 months).

### **Analysis of secondary outcomes**

#### **Point prevalence and outcome of patients with positive ADA at baseline visit in cohort-1**

Positive ADA were detected in 30 patients (11.3%, 16 females) at baseline visit (first infusion of CT-P13). All these patients had undetectable infliximab trough levels ( $<0.30$   $\mu\text{g/mL}$ ). Among these 30 patients, 15/135 had axSpA (11%), 6/31 RA (19%), 7/64 IBD (11%) and 2/21 PSa (10%). No significant association was observed between presence of ADA and age, gender, type of disease and concomitant methotrexate or other conventional synthetic disease modifying anti-rheumatic drugs (DMARDs). No association was observed between ADA detection and treatment with methotrexate after adjustment to disease type. Patients with positive ADA at baseline visit were more likely to have a BMI  $>30$  (14/30, 45% vs. 40/235, 17%,  $p<0.001$ ) and received less innovator infliximab infusions ( $28\pm 20$  vs.  $40\pm 25$  infusions,  $p=0.012$ ) than patients with negative ADA.

Among these 30 patients, 13 (43%) discontinued infliximab during the observation period (11 treated with CTP-13 and 2 with innovator infliximab), due to loss of efficacy (n=10), side effects (n=2 infusion-related reactions) and diagnosis of neoplasia (n=1). 12 of these patients switched from CT-P13 to SB2, which was maintained until the end of the observation period. Interestingly, 7 of these patients had gradual conversion to seronegative status, with parallel increase of infliximab trough levels, whereas ADA seropositivity persisted in 5 patients with undetectable infliximab trough levels.

In addition, 5 patients were maintained with innovator infliximab up to the end of the observation period with a good clinical response according to their treating physician, despite all of them had constant positive ADA detection and undetectable infliximab trough levels (<0.30 ug/mL).

#### **Influence of the successive switches to biosimilars on the risk of immunogenicity**

Kaplan Meyer curves illustrating ADA-free survival of the 235 ADA negative patients at baseline from cohort-1 showed no influence of the number of received INF biosimilars on ADA development during the observation period (**Figure 2**).

In cohort-2, among the 29/44 (66%) CTP13-treated patients who switched to SB2, only a single patient developed ADA (**Figure 1B**).

#### **Factors associated with ADA generation**

No predictive factor of immunogenicity was identified in cohort-1, including type of disease, age, sex, BMI or concomitant methotrexate or other conventional synthetic DMARD intake. In cohort-2, a BMI >30 at baseline visit and mean infliximab through levels <2 ug/mL from baseline visit to seroconversion were predictive of the development of ADA with Hazard

Ratio (95% confidence interval, CI) of 5.54 (1.30-23.65) and 5.53 (1.30-23.43), respectively (Table S2).

### **Influence of immunogenicity on treatment maintenance**

#### **Cohort-1**

The risk of treatment discontinuation was significantly higher in patients with positive ADA at baseline visit or during follow-up compared to patients without ADA (Hazard Ratio 2.37, 95% confidence interval 1.38-4.05,  $p=0.002$ ) (Figure 3A). Moreover, patients who discontinued infliximab ( $n=60$ ) were more likely to have positive ADA (20/60, 33%) compared to patients still treated with infliximab (30/205, 15%) ( $p=0.002$ ).

Among the 26 patients who discontinued infliximab because of primary or secondary loss of efficacy, 12 had positive ADA. Four patients stopped infliximab because of an infusion-related reaction, and all of them were ADA positive.

#### **Cohort-2**

The risk of treatment discontinuation was also significantly higher in patients with positive ADA during the observation period compared to patients without ADA (Hazard Ratio 2.79, 95% confidence interval 1.04-7.52,  $p=0.042$ ) (Figure 3B). Among the 10 patients who stopped infliximab because of primary or secondary loss of efficacy, 4 were tested positive for ADA. Two patients stopped their treatment because of an infusion-related reaction, and both were tested positive for ADA.

### **Retention rate of biosimilar infliximab at the end of the observation period**

The retention rate of biosimilar infliximab in cohort-1 was 58% (155/265) at the end of observation period, including 132 patients treated with SB2 and 23 who remained treated with CT-P13 (Figure S1A).

The retention rate of biosimilar infliximab in cohort-2 was 66% (29/44) at the end of observation period, including 24 patients treated with SB2 and 4 who were treated with CT-P13 (**Figure S1B**).

### **Meta-analysis integrating our results to data collected from a systematic literature search**

The selection of studies included in the meta-analysis is summarized in **Figure S2 and Table S3**. Out of 263 articles identified, 16 were finally included, representing a total of 2979 patient. We identified 6 studies (1 RCT and 5 observational studies) that analyzed the incidence of ADA development after the switch from innovator infliximab to CTP-13, representing 971 patients. The pooled incidence of ADA occurrence in this population was 5.2% (95% CI 2.8-8.3%). This result was based on random effects model because of significant heterogeneity (Cochran  $Q=16.53$  for 5 degrees of freedom, DF,  $p=0.006$ ). After removing the RCT, the pooled incidence was 3.8% (95% CI 2.6-5.2%) and no heterogeneity was observed ( $Q=3.09$  for 4 DF,  $p=0.543$ ). After inclusion of our results obtained from cohort-1, the incidence was 4.7% (95% CI 3.5-6.1%; **Figure 4A**), with no significant heterogeneity ( $Q=10.9$  for 5 DF,  $p=0.052$ ).

Twelve studies assessed the occurrence of ADA in innovator infliximab-naive patients that received CPT-13, representing 2008 patients. The pooled incidence of ADA occurrence in this population was 28% (95% CI 17.8-39.2). This result was also based on random effects model because of substantial heterogeneity (Cochran  $Q=320$  for 11 DF,  $p<0.001$ ). When considering observational studies, and after inclusion of our results obtained from cohort-2, the incidence was 21.1% (95% CI 13.1-30.3%; **Figure 4B**), with reduced but still significant heterogeneity ( $Q=11.02$  for 3 DF,  $p=0.012$ ). When considering RCTs, the incidence was 30.7% (95% CI 18.2-44.9%) with substantial heterogeneity ( $Q=289$  for 8 DF,  $p<0.001$ ).

## DISCUSSION

Our study brings some original and relevant specificities, including the inclusion of patients that received 3 different infliximab molecules, allowing the demonstration of a comparable immunization rate regardless of the number of biosimilars received. In addition, patients were followed during observation period of 3 years, which is longer than in most previous studies. We also assessed the mean time to ADA detection, which was  $21.19 \pm 13.7$  months in cohort-1 and  $12.8 \pm 10.8$  months in cohort 2, supporting that ADA seroconversion occurs during the first months in infliximab-naive patients.

The rate of ADA seroconversion was 8.5% in patients receiving biosimilars Infliximab who were previously receiving the original molecule. In previous studies assessing the switch from innovator to biosimilar Infliximab, this rate varied from 2.4% to 14.8%, [6, 16-18] and the pooled incidence was 4.7% in our meta-analysis. This is concordant with our results, considering also the variability of diagnoses, patients' characteristics, concomitant immunosuppressive therapies and treatment duration. Moreover, the successive use of 2 biosimilars in our cohort did not increase the risk of immunogenicity compared to previous studies that analyzed the use of a single biosimilar only. PLANETRA and PLANETAS studies found higher immunization rates: 44.8% and 27.4% at 48 weeks after the switch, respectively, [2-3] but they include patients already immunized at baseline. Including patients with positive ADA at baseline visit, the rate of immunization in cohort 1 was 19%, close to what was observed in PLANETAS, considering that the majority of patients had axSpA in our cohort. These results are reassuring for clinical practice in case of interchangeability between innovator to biosimilars, as reported in the literature. [5-7, 16-23]

The rate of ADA seroconversion was 25% in infliximab-naive patients who received biosimilars Infliximab during the observation period. In the literature, immunization rates ranged from 8.0% to 62.4% in this population and the pooled incidence was 21% in our meta-

analysis of observational studies.[24-25] These measures were highly variables across studies since they depended of the study power, patients' characteristics or methods of ADA detection. We observed a higher rate of ADA seroconversion in cohort-2 compared to cohort-1. This difference may partly be explained by the exclusion of the 30 patients with positive ADA at baseline visit in cohort-1. Thus, we followed patients who did not developed ADA within a long exposition period upon innovator infliximab, and these patients may have a lower probability of further having ADA, given that ADA seroconversion usually occurs during the first months of treatment.

BMI>30 was associated with ADA positivity at baseline visit in cohort-1 and predicted ADA seroconversion in cohort-2. The impact of high BMI on ADA development and reduction of anti-TNF- $\alpha$  efficacy has already been reported. A higher BMI could be responsible of an inflammatory role of fat tissues by the production of multiple pro-inflammatory cytokines.[26-28] Thus, this parameter is primordial and needs to be taken into account in clinical practice, by tighter monitoring or dose adaptation, in order to avoid treatment discontinuation.

In cohort-2, a low concentration of infliximab trough serum levels was predictive of ADA seroconversion. This is consistent with previous data showing a reduced risk of immunization with higher doses of infliximab, leading to increased infliximab trough serum levels.[7, 8, 29] Concomitant treatment with Methotrexate or other conventional synthetic DMARDs was not found as a potent protective factor of immunogenicity in both cohorts, considering the entire population of after adjustment to disease type, illustrating the disparate findings of previous study results about the protective role of these treatments on immunogenicity.[8, 30-34] However, in cohort 2, a non-significant trend for a protective effect of MTX was observed, and the absence of significativity may be explained by the limited sample size of this cohort.

Patients with ADA had an increased risk of treatment discontinuation, which was mainly due to primary or secondary lack of efficacy. Of note, a subset of patients who interrupted infliximab because of insufficient efficacy were tested negative for ADA (14 in cohort 1, 6 in cohort 2), suggesting either a failure of the mechanism of action of TNF- $\alpha$  inhibitors or a potential lack of sensitivity of the assay. Infusion-related reactions were not frequently observed (4 in cohort-1, 2 in cohort-2), and all occurred in patients with positive ADA, as previously reported.[7, 20, 35, 36] It is important to note that physicians were not blinded for ADA status, and ADA positivity may have influenced the choice of treatment discontinuation. The retention rates of patients treated by biosimilars were 58% in cohort-1 and 55% in cohort-2 at the end of the observation period. The retention rates were 66% at 2 years in patients suffering from inflammatory bowel diseases,[16] 44% at 2 years in PLANETRA,[20] and 64,8% in PLANETAS,[21] and differences with our study may be related to variable observation periods and inclusion of a larger panel of chronic inflammatory disorders.

Our study is limited by the small size of the second cohort, making difficult to compare across disease populations. Patients from cohort-1 were all correctly controlled with innovator infliximab before the switch. Therefore, our results may not be extrapolated to a random population of patients who receive biosimilar infliximab or who are inadequately managed with innovator infliximab. Being observational, our study lacks the proper control of continuing originator infliximab ,without switching to biosimilars infliximab, in to provide framework to the observations noted. Moreover, we had insufficient data to robustly examine the relationship between doses of infliximab and ADA generation.

ADAs were detected only in patients with undetectable infliximab trough levels and patients with detectable infliximab trough levels all have negative ADAs, which may suggest that the presence of the drug may interfere with the detection of antibodies.

In summary, our study shows that immunogenicity occurrence is not favored by the switch to biosimilars infliximab. However, our data highlight that consequences of immunogenicity are not negligible, with increased risk of allergic reactions and treatment discontinuation.

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**TABLES AND FIGURES:**

**Table 1: Description of cohorts 1 and 2**

	<b>Cohort-1 (n=265)</b>	<b>Cohort-2 (n=44)</b>
<b>Age (years), mean±SD</b>	47±16	59±9
<b>Gender, females n (%) / males n (%)</b>	120 (45) / 145 (55)	19 (43) / 25 (57)
<b>Disease duration, years, mean±SD</b>	15±11	7±6
<b>Weight (kg) mean±SD</b>	73±17	74±17
<b>Body mass index (kg/m<sup>2</sup>), mean±SD</b>	26.6±5.5	26.7±6.1
<b>Disease, n (%)</b>		
<b>axSpA</b>	135 (51)	20 (45.5)
<b>IBD</b>	64 (24)	9 (20.5)
<b>RA</b>	31 (12)	9 (20.5)
<b>PsA</b>	22 (8)	4 (9)
<b>Uveitis</b>	8 (3)	0 (0)
<b>Other</b>	5 (2)	2 (4.5)
<b>Concomitant treatment with:</b>		
<b>MTX, n (%)</b>	96 (36)	23 (52)
<b>Leflunomide n (%)</b>	39 (15)	4 (9)
<b>Azathioprine, n (%)</b>	6 (2)	2 (5)
<b>Duration of treatment with innovator INF (months), mean±SD</b>	70±59	
<b>Number of infusions, mean±SD</b>	36±28	
<b>Dose of the last infusion (mg), mean±SD</b>	407±152	

*RA: Rheumatoid Arthritis, IBD: Inflammatory Bowel Diseases, axSpA: axial spondyloarthritis, PsA: Psoriatic Arthritis*

**Table 2: Distribution and outcome of patients during the observation period**

	AxSpA	IBD	RA	PsA	Uveitis	Other CID
<b>COHORT-1</b>						
INCLUSION (n=265)	135	64	31	22	8	5
<b>December 2017</b>						
- Switch CT-P13-SB2 (n=140), n (%)	72 (53.5)	38 (59)	15 (49)	9 (41)	3 (37.5)	3 (60)
- CT-P13 (n=26), n (%)	11 (8)	6 (9)	4 (13)	4 (18)	1 (12.5)	0 (0)
- Re-established with innovator INF (n=55), n (%)	38 (28)	3 (5)	7 (22)	6 (27)	0 (0)	1 (20)
- Treatment interruption, n (%)	14 (10.5)	17 (27)	5 (16)	3 (14)	4 (50)	1 (20)
<b>End of observation period</b>						
- Patients treated with SB2 (n=131), n (%)	67 (50)	38 (59)	14 (45)	8 (36)	2 (25)	2 (40)
- Patients treated with CT-P13 (n=23), n (%)	9 (7)	6 (9)	4 (13)	3 (14)	1 (12.5)	0 (0)
- Patients treated with innovator INF (n=37), n (%)	27 (20)	2 (4)	4 (13)	3 (14)	0 (0)	1 (20)
- Treatment interruption, n (%)	32 (23)	18 (28)	9 (29)	8 (36)	5 (62.5)	2 (40)
<b>COHORT-2</b>						
INCLUSION (n=44)	20	9	9	4	0	2
<b>December 2017</b>						
Switch CT-P13-SB2 (n=29), n (%)	11 (55)	8 (89)	7 (78)	1 (25)	0 (0)	2 (100)
CT-P13 (n=5), n (%)	3 (15)	1 (11)	0 (0)	1 (25)	0 (0)	0 (0)
Treatment interruption, n (%)	6 (30)	0 (0)	2 (22)	2 (50)	0 (0)	0 (0)
<b>End of observation period</b>						
Patients treated with SB2 (n=131), n (%)	10 (50)	7 (78)	5 (56)	1 (25)	0 (0)	2 (100)
Patients treated with CT-P13 (n=23), n (%)	2 (10)	1 (11)	0 (0)	1 (25)	0 (0)	0 (0)
Treatment interruption, n (%)	8 (40)	1 (11)	4 (44)	2 (50)	0 (0)	0 (0)

*RA: Rheumatoid Arthritis, IBD: Inflammatory Bowel Diseases, axSPA: axial spondyloarthritis, PsA: Psoriatic Arthritis, CID: chronic inflammatory disease*

### **Figure Legends:**

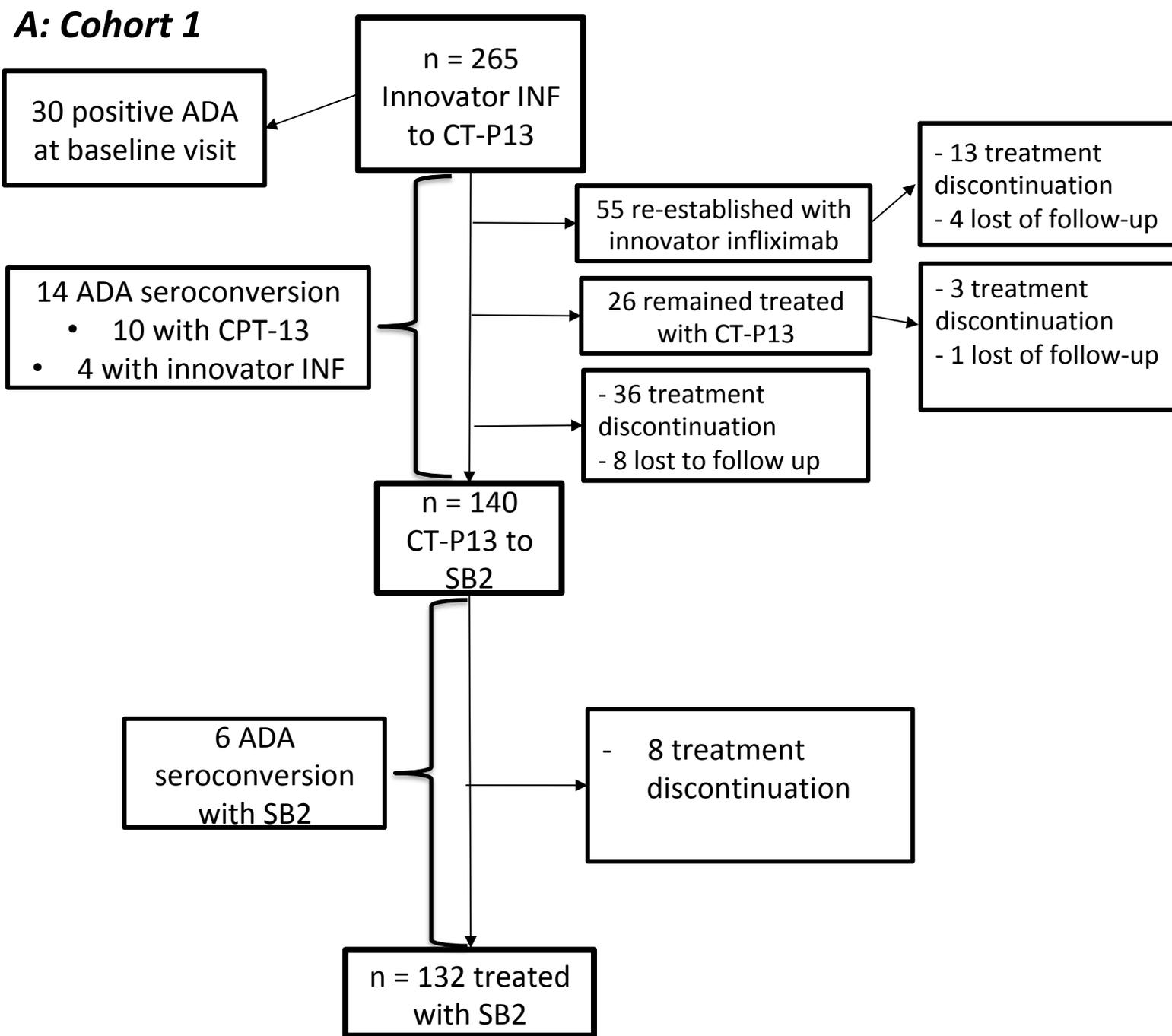
**Figure 1:** Flow Chart illustrating the switch to the different biosimilars infliximab (INF: Infliximab)

**Figure 2:** Immunogenicity-free survival illustrating the influence of the number of received INF biosimilars on immunogenicity in cohort-1, in the 235 patients ADA-free at baseline

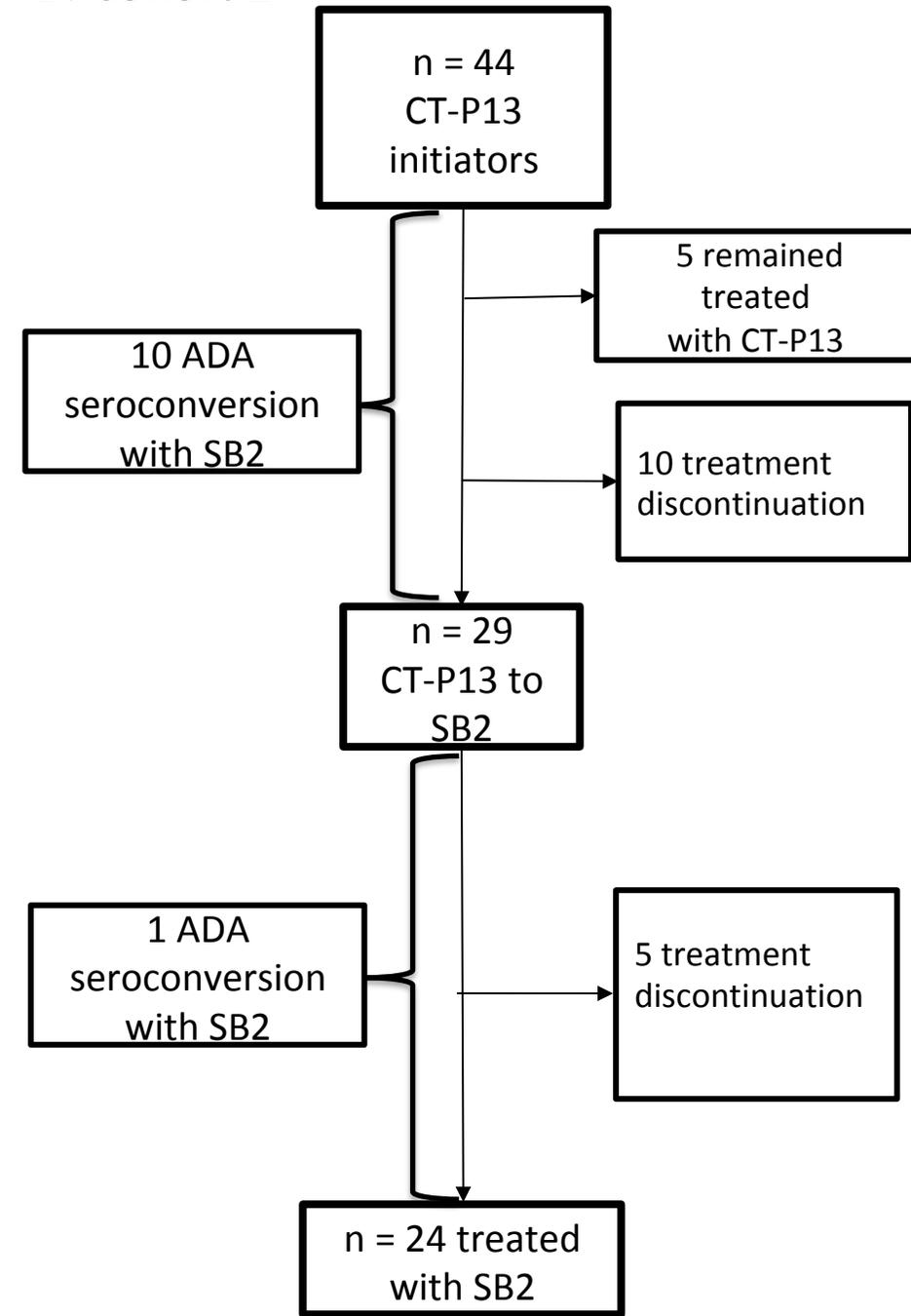
**Figure 3:** Influence of immunization on treatment discontinuation in cohort-1 (A) and cohort-2 (B) (FU: Follow-up)

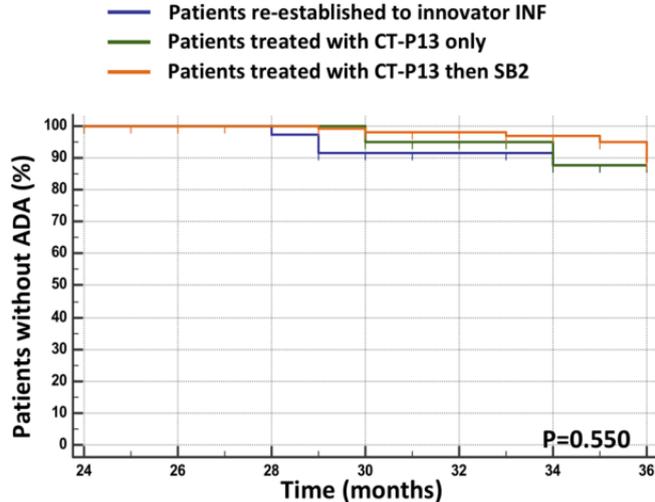
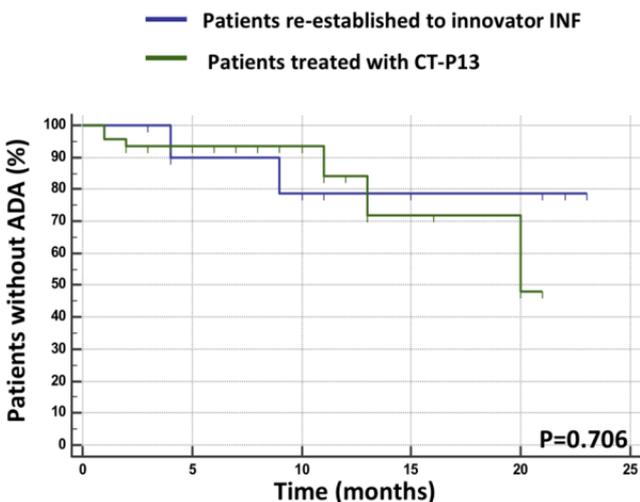
**Figure 4:** forest plots illustrating the meta-analysis of observational studies of the incidence of ADA development after the switch from innovator infliximab to CTP-13 (A) and the incidence of ADA development in patients who were initiated with a biosimilar infliximab (B).

### A: Cohort 1



### B: Cohort 2





Switch from innovator INF to CT-P13



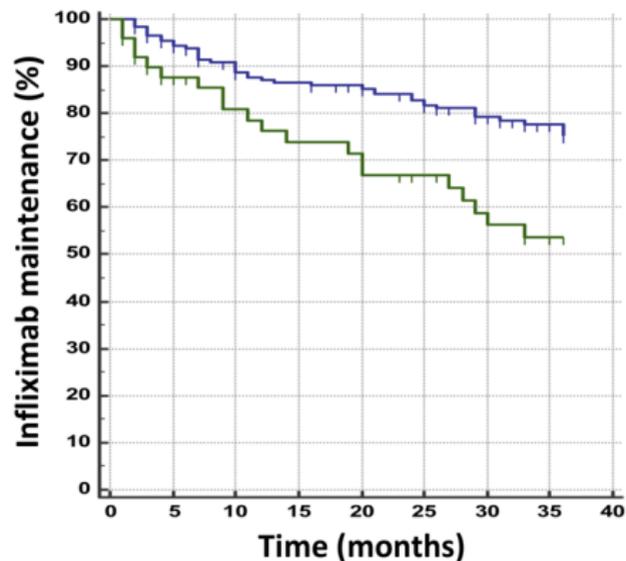
Biosimilars	Baseline n	Baseline to 12 months		12 to 24 months		24 to 36 months	
		ADA+ n (%)	n patients still in the study at 12 months	ADA+ n (%)	n patients still in the study at 24 months	ADA+ n (%)	n patients at the end of the study
Innovator INF	0	0 (0)	40	0 (0)	36	4 (13)	31
CTP-13 only	235	6 (4)	145	2 (1.5)	140	2 (10)	21
CTP13 then SB2	0	0 (0)	0	0 (0)	0	6 (5)	111
Total	235	6 (3)	185	2 (1)	176	12 (7)	163

Switch from CT-P13 to SB2



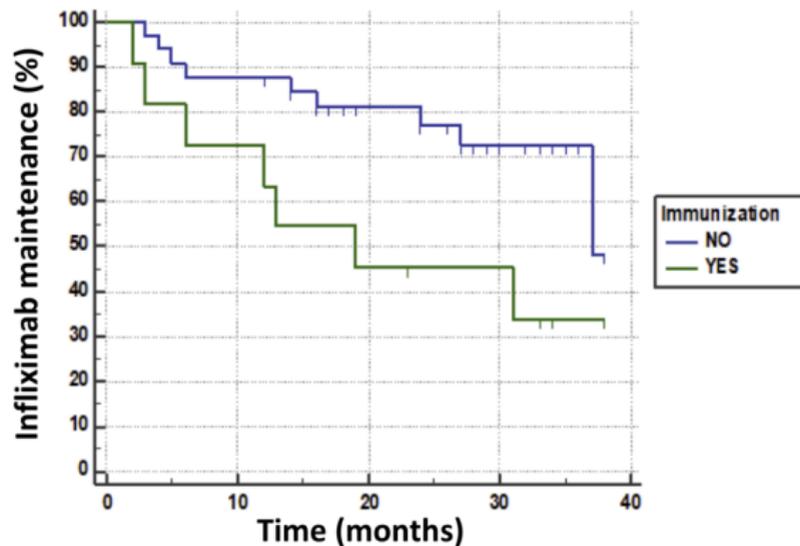
A

Cohort 1



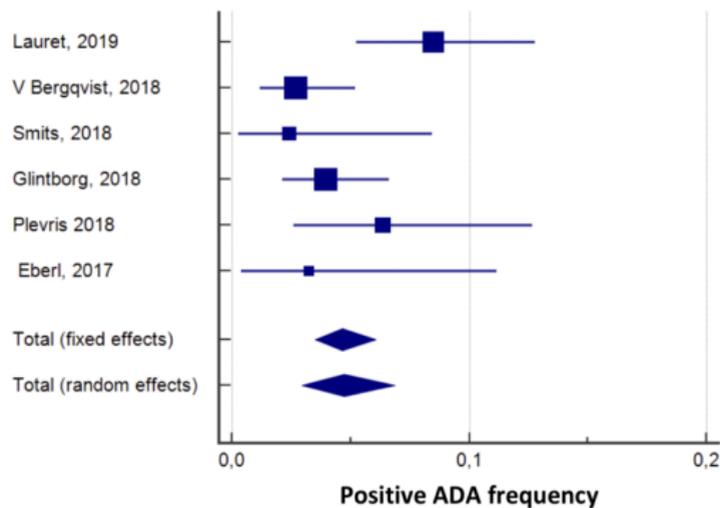
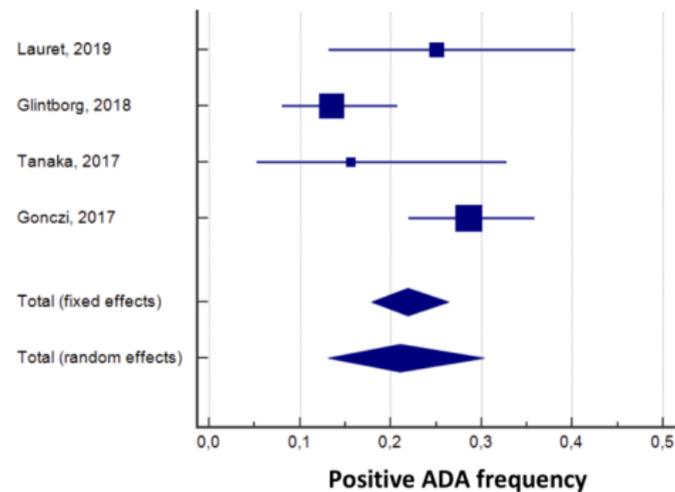
B

Cohort 2



ADA status	Baseline to 12months		12 to 24 months		24 to 36 months	
	Treatment interruption n (%)	n patients still in the study at 12 months	Treatment interruption n (%)	n patients still in the study at 24 months	Treatment interruption n (%)	n patients at the end of the study
ADA -	23 (13)	180	6 (3)	174	11 (7)	163
ADA+ (baseline + FU)	10 (26)	39	5 (15)	34	5 (17)	29
<b>Total</b>	<b>33 (15)</b>	<b>219</b>	<b>11 (5)</b>	<b>208</b>	<b>16 (8)</b>	<b>192</b>

ADA status	Baseline to 12months		12 to 24months		24 to 36 months	
	Treatment interruption N (%)	N patients still in the study at 12 months	Treatment interruption N (%)	N patients still in the study at 24 months	Treatment interruption N (%)	N patients at the end of the study
ADA -	4 (13)	29	3 (12)	26	2 (8)	24
ADA+ (baseline + FU)	4 (57)	7	2 (40)	5	0 (0)	5
<b>Total</b>	<b>8 (22)</b>	<b>36</b>	<b>5 (16)</b>	<b>31</b>	<b>2 (7)</b>	<b>29</b>

**A****B**

Study	Proportion (%)	95% CI	Weight (%)	
			Fixed	Random
Lauret, 2019	8,475	5,253 to 12,785	21,07	20,09
V Bergqvist, 2018	2,685	1,166 to 5,221	26,58	21,82
Smits, 2018	2,410	0,293 to 8,435	7,47	11,82
Glintborg, 2018	3,939	2,114 to 6,642	29,42	22,55
Plevris, 2018	6,364	2,597 to 12,673	9,87	13,98
Eberl, 2017	3,226	0,393 to 11,172	5,60	9,74
Total (fixed effects)	4,665	3,508 to 6,065	100,00	100,00
Total (random effects)	4,734	2,974 to 6,878	100,00	100,00

Study	Proportion (%)	95% CI	Weight (%)	
			Fixed	Random
Lauret, 2019	25,000	13,193 to 40,338	11,81	21,43
Glintborg, 2018	13,492	8,060 to 20,721	33,33	29,11
Tanaka, 2017	15,625	5,275 to 32,788	8,66	18,66
Gonczy, 2017	28,571	22,009 to 35,876	46,19	30,79
Total (fixed effects)	21,889	17,838 to 26,383	100,00	100,00
Total (random effects)	21,059	13,139 to 30,271	100,00	100,00