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Perioperative treatment with TNF inhibitors does not affect survival of total hip arthroplasty in inflammatory arthritis: A registry-based cohort study

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ABSTRACT

Objectives: Aim of this study was to investigate the effect of perioperative exposure to TNF inhibitors (TNFi) on the long-term survival of total hip arthroplasty (THA) in inflammatory arthritis patients from a large regional register of arthroplasty procedures (RIPO).
Methods: This study is a retrospective analysis of data from RIPO for THAs performed between 2008 and 2019. After extraction of the procedures of interest from the RIPO dataset, cross-matching with administrative databases were used to identify patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), primary osteoarthritis (OA), and treatments of interest. Three different cohorts of patients were identified: perioperative TNFi-treated patients (6 months before or after the surgery), perioperative non-bDMARD/tsDMARD (biologic or targeted-synthetic disease modifying antirheumatic drugs), and OA.
Results: At an average follow-up of 5 years, survival rates (using any revision surgery as an endpoint) were not significantly different when perioperative TNFi users and non-bDMARD/tsDMARD patients were compared ($p = 0.713$), and between TNFi-treated and OA controls ($p = 0.123$). At the latest available follow-up, 2.5% patients in the TNFi cohort, 3% in the non-bDMARD/tsDMARD cohort, and 0.8% in the OA cohort underwent revision surgery. No significant differences were found comparing the risk of postoperative infection or aseptic loosening among groups.
Conclusion: Risk of revision surgery is not increased in patients with inflammatory arthritis perioperatively exposed to TNFi. Our results support the long-term safety of this class of molecules on survival of prosthetic implants.

Introduction

Inflammatory arthritis is an umbrella term encompassing a range of immune-mediated joint diseases sharing common clinical features such as synovitis, tenosynovitis, enthesitis and a variable prevalence of extra-articular manifestations. Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) represent the most common chronic inflammatory arthritis, affecting an overall estimate of nearly 1% of the general population [1–3].

Since their approval in the late 90^s, tumor necrosis factor inhibitors (TNFi) have revolutionized the treatment of inflammatory arthritis and now are the most used class of biologic disease modifying antirheumatic drugs (bDMARDs) [4]. TNFi represent a safe therapeutic option in patients with RA, PsA and AS although burdened by an increased risk of infections [5–7], including septic arthritis [8].

Regardless the advent of TNFi and other novel therapeutics, in a significant proportion of patients, uncontrolled inflammation still leads to joint damage and eventual destruction [9] with a profound impact on quality of life [10] and on the risk of permanent disability [11]. Indeed, despite a clear decreasing trend, RA patients have a four times higher probability of receiving joint replacement surgery [12]; moreover, their lifetime risk of total hip arthroplasty (THA) and total knee arthroplasty

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(TKA) is estimated to be 22% and 17%, respectively, with higher risk observed when the disease arises in younger ages [13].

Furthermore, patients with arthritis are considered at higher risk of complications following arthroplasty [14], including prosthetic joint infection, which is the leading cause of revision surgery in this patients' population [15,16]. Although the short-term risk of infectious complications seems not increased in TNFi recipients [17], perioperative exposure to TNFi has been associated with a 2.5 increased odds of surgical site infection following arthroplasty surgery [18], and with the development of severe postoperative orthopedic infections [19]. For this reason, temporary discontinuation of TNFi is considered a safe approach in the perioperative period of arthritis patients undergoing total joint arthroplasty [20].

On the other hand, TNF inhibition is expected to exert also beneficial effects on the outcomes of arthroplasty surgery in inflammatory arthritis patients because it can counteract the physiopathology of aseptic loosening and bone reabsorption, common causes of surgical revision after THA and TKA [21].

On these premises, aim of this study was to investigate the effect of perioperative exposure to TNFi on the long-term survival of THA in inflammatory arthritis patients from a large registry of arthroplasty procedures.

Methods

Study design and data sources

The present study is based on the data of a regional registry-based retrospective cohort, the Emilia-Romagna Orthopedic Arthroplasty Implants Register (Registro Implantologia Protesica Ortopedica, RIPO) [22]. The RIPO register, founded in 1990, systematically collects data from hip, knee and shoulder arthroplasty procedures performed in 62 public or private orthopedic departments within the Emilia-Romagna region (4.5 million inhabitants). The capture rate is approximately 95% [22]. The design of this register, which is a member of the International Society of Arthroplasty Registries, was conceived to allow the comparison with the most important national registries worldwide [23].

Baseline data include age, gender, body mass index (BMI), and clinical history of the patient; diagnosis leading to joint replacement; model and design of the implant; surgeon performing the procedure, and in which hospital. Furthermore, the same information is collected in case of revision surgery; of note, data are captured even if an Emilia-Romagna inhabitant receives revision surgery outside the region: indeed, according to the Italian National Health System (Sistema Sanitario Nazionale, SSN), all surgical procedures performed in any part of Italy are notified and billed back to the region of residence of the patient. All data are entered by the surgeon at the end of the procedure. No information is collected about postoperative care, rehabilitation process or clinical scores. Primary endpoint is revision of one or more of the implant components.

The extraction from the global database was made on July 2022 and the initial inclusion criteria was primary THA performed between January 2008 and July 2019. The date of January 2008 was chosen based on the first TNFi prescription available from database, which is dated back to 2007. A total of 61,811 primary hip replacement procedures were performed in Emilia-Romagna during the selected period; only the first THA surgery for each patient was included. All the procedures performed on patients living outside Emilia-Romagna were excluded, to minimize bias due to loss at follow-up.

After extraction of the procedures of interest from the RIPO dataset, cross-matching with regional co-payment exemption database was used to identify patients with RA, PsA and AS. In Italy, when the diagnosis of a specific chronic disease is made, patients are deemed eligible for co-payment exemption. All residents entitled to co-payment exemption are included in dedicated regional registries and are exonerated from financial contribution to clinical and therapeutic activities related to the specific disease. Strict rules are applied for issuing co-payment exemptions. The diagnosis must be confirmed by a consultant rheumatologist working in a public (SSN) referral center based on a comprehensive clinical, laboratory and instrumental assessment. Furthermore, the co-payment exemption for chronic rheumatic diseases does not expire and it is not subject to renewability. All patients entitled to co-payment exemption codes specific for RA (code 006.714.X), PsA (045.696.0) and AS (054.720.0) were included in the present study.

A similar approach was applied to identify treatments of interest by cross-matching with the pharmaceutical territorial assistance (PTA) database which systematically store information on every single prescription of drugs directly dispensed by the SSN, including those used in patients with inflammatory arthritis. Every time a patient picks up a medication from a public or private pharmacy following a prescription released from a SSN physician, regardless of location (e.g., another Italian region), an event is recorded in the Emilia-Romagna PTA database. Indeed, according to the Italian laws, the cost of the prescription is notified and billed back to the region of residence of the patient; of note, bDMARD and targeted-synthetic DMARDs (tsDMARD) are released only upon prescription from a specialized SSN physician and cannot be purchased directly from the patient without prescription or using a prescription released from a physician not working in the SSN.

The co-payment exemption registry and the PTA database were then used to define specific patients' cohorts as described in the following paragraph. Furthermore, the PTA database was used to ascertain the concurrent usage of conventional synthetic DMARDs (csDMARD) or systemic corticosteroids during the 3 months preceding surgery.

Ethical approval for the study was not required as registry studies are covered by the informed consent signed at treatment. All sensitive data were handled in pseudo-anonymized format, with all identity information removed. The study complies with the Declaration of Helsinki and its latest amendments.

Definition of the study cohorts

Based on the above-mentioned methodology, three different cohorts of patients were identified:

a) **Perioperative TNFi-treated patients (cohort A):** all patients entitled to co-payment exemption for RA, PsA and AS treated with any of the approved TNFi (L04AB02 infliximab; L04AB04 adalimumab; L04AB01 etanercept; L04AB06 golimumab; L04AB05 certolizumab pegol) with at least one prescription in the 6 months preceding AND in the 6 months following surgery;
b) **Perioperative non-bDMARD/tsDMARD (cohort B):** all patients entitled to co-payment exemption for RA, PsA and AS who never received TNFi or any other bDMARD or ts-DMARD (L01XC02 rituximab; L04AA14 anakinra; L04AA24 abatacept; L04AA26 belimumab; L04AA29 tofacitinib; L04AA32 apremilast; L04AA37 baricitinib; L04AA44 upadacitinib; L04AA45 filgotinib; L04AC05 ustekinumab; L04AC07 tocilizumab; L04AC08 canakinumab; L04AC10 secukinumab; L04AC13 ixekizumab; L04AC14 sarilumab);
c) **Primary osteoarthritis (OA) (cohort C):** patients who were included in the RIPO with OA as the primary diagnosis for THA; not entitled to any exemption for the abovementioned inflammatory joint diseases or who never received any TNFi, bDMARD or ts-DMARD.

The entire process of patients' selection is summarized in Fig. 1.

Statistical analysis

Given the registry-based design of our study, no power calculation was performed. In particular, a priori power calculation was not performed because there was no sampling as the RIPO registry entire population was taken into account. On the other hand, several articles

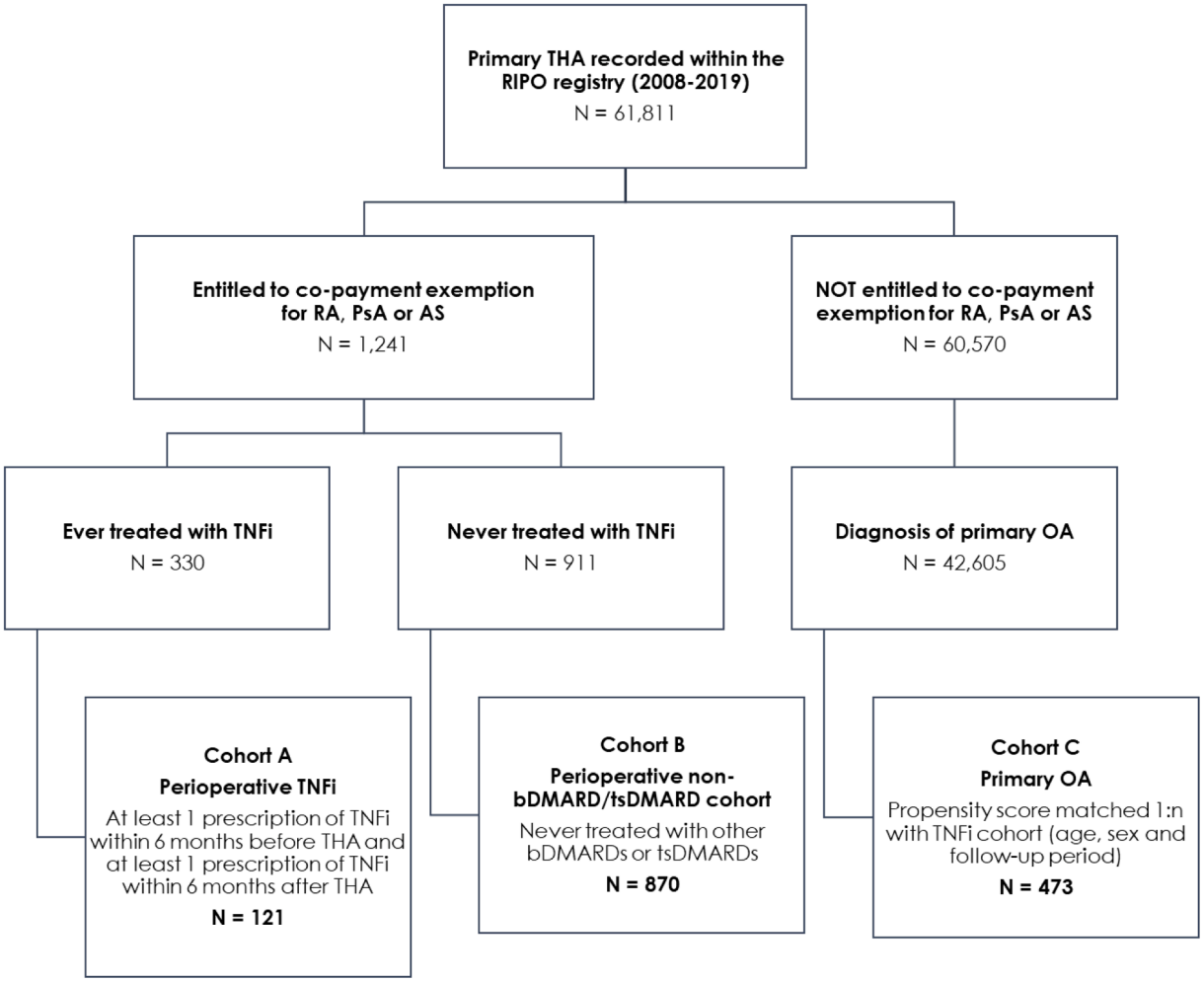


Fig. 1. Patients' selection process. AS, ankylosing spondylitis; bDMARD, biologic disease modifying antirheumatic drug; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RIPO, registro implantologia protesica ortopedica; THA, total hip arthroplasty; TNFi, TNF inhibitors; tsDMARD, targeted-synthetic disease modifying antirheumatic drug.

support the notion that post-hoc power calculations are never appropriate, as it is already known with certainty whether or not a statistically significant finding has occurred [24–26].

Data are expressed as mean ± standard deviation, median [25th-75th percentile] or number (percentage) as appropriate. For comparison, we generated a 1:n matched with the TNFi cohort from the individuals with primary OA enrolled in the RIPO registry, using the propensity score, as previously described [27]. The covariates entered in the propensity score were gender, age class at THA and follow-up duration.

Continuous variables were compared between groups using Student's *t*-test; Fisher's exact test was used to detect differences in dichotomic variables. The survival rates of implants were calculated and plotted according to the Kaplan-Meier method. The endpoint was surgical revision, defined as the removal or change of any component of the implant, due to complication. The log-rank test was employed to detect differences between different survival curves. Statistical analyses were performed with the use of JMP®, Version 12.0.1. (SAS Institute Inc., Cary, NC, 1989–2007) and R version 3.4.2. (Comprehensive R Archive Network), with statistical significance defined as $p < 0.05$ [28].

Data statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Results

General characteristics of the study population

General characteristics of the study cohorts are reported in Table 1. The perioperative TNFi-treated cohort included 121 patients; the cohort of patients not exposed to bDMARD/tsDMARD consisted of 870 patients and the primary OA cohort included 473 patients.

Of note, on the overall cohort of 330 patients ever treated with TNFi, only 17 received a prescription of TNFi in the 6 months preceding surgery but not in the 6 months following surgery; however, 6 of them received a TNFi prescription after the first 6 months post-surgery: none of these patients underwent revision surgery although one individual with PsA was admitted to hospital for delayed surgical wound healing not requiring surgery. Of the remaining 11 patients, 4 received a new prescription of a non-TNFi bDMARD in the 6 months following surgery while the other patients did not receive any bDMARD/tsDMARD prescription until the end of the study period. On the other hand, 14 patients had a prescription in the 6 months following surgery but not before surgery.

Significant differences were found between TNFi and non-bDMARD/tsDMARD-treated patients regarding age (60.5 ± 12.2 vs 67.0 ± 10.5 years, $p<0.001$), and number of patients with AS (17.4% vs 4.3%, $p<0.001$) and RA (52.9 vs 66.6%, $p = 0.013$). No significant differences were detected regarding BMI and perioperative use of glucocorticoids or

Table 1
General characteristics of the study cohorts.

	Cohort A: Perioperative TNFi	Cohort B: Perioperative non-bDMARD/tsDMARD	Cohort C: Primary OA	*p* value A vs B	*p* value A vs C
N° of implants	121	870	473	–	–
Age, years	60.5 ± 12.2	67.0 ± 10.5	63.3 ± 11.0	<0.001	0.018
Age class					
<40 years	6 (5.0)	19 (2.2)	10 (2.1)	0.780	0.954
40–49 years	15 (12.4)	37 (4.3)	42 (8.9)	0.002	1.000
50–59 years	30 (24.8)	107 (12.3)	119 (25.2)	0.002	1.000
60–69 years	42 (34.7)	288 (33.1)	161 (34.0)	1.000	1.000
70–79 years	28 (23.1)	353 (40.6)	118 (24.9)	0.002	1.000
>80 years	0 (0.0)	66 (7.6)	23 (4.9)	0.019	0.163
Female gender, n (%)	78 (64.5)	579 (66.6)	301 (63.6)	1.000	1.000
BMI category*					
Underweight, n (%)	1 (0.9)	11 (1.5)	7 (1.8)	1.000	1.000
Normal weight, n (%)	50 (45.0)	257 (36.1)	108 (27.8)	0.350	0.004
Overweight, n (%)	35 (31.5)	302 (42.4)	174 (44.8)	0.156	0.066
Obesity, n (%)	25 (22.5)	142 (19.9)	99 (25.5)	1.000	1.000
Specific rheumatic disease					
RA, n (%)	64 (52.9)	579 (66.6)	–	0.013	–
PsA, n (%)	36 (29.8)	254 (29.2)	–	1.000	–
AS, n (%)	21 (17.4)	37 (4.3)	–	<0.001	–
Perioperative anti-rheumatic medications					
Etanercept, n (%)	55 (45.5)	–	–	–	–
Adalimumab, n (%)	43 (35.5)	–	–	–	–
Infliximab, n (%)	9 (7.4)	–	–	–	–
Certolizumab pegol, n (%)	9 (7.4)	–	–	–	–
Golimumab, n (%)	5 (4.1)	–	–	–	–
Corticosteroids, n (%)	22 (18.2%)	185 (21.3%)	67 (14.2)	1.000	<0.001
csDMARDs, n (%)	26 (21.5%)	130 (14.9%)	1 (0.2)	0.342	<0.001
Corticosteroids + csDMARDs, n (%)	40 (33.1%)	244 (28.0%)	4 (0.8)	1.000	<0.001
Follow-up, years	5.3 ± 3.3	5.0 ± 3.3	5.6 ± 3.3	0.367	0.407
Implants at risk at 5 years, n (%)	60 (49.6)	409 (47.0)	250 (52.9)	–	–

Legend: AS, ankylosing spondylitis; BMI, body mass index; bDMARD, biologic disease-modifying antirheumatic drug; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, TNF inhibitors; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

* 17.3% missing data.

csDMARDs. On the other hand, the propensity score-matched OA cohort had higher average age compared to the TNFi cohort (60.5 ± 12.2 vs 63.3 ± 11.0 years, $p = 0.018$) although the age class distribution did not differ among the two cohorts.

Implants survival rate

At an average follow-up of 5 years, survival rates (using any revision surgery as endpoint) were not significantly different when perioperative TNFi users and non-bDMARD/tsDMARD patients were compared [5-year survival 96.6% (89.6–98.9) vs 97.1% (95.6–98.2), $p = 0.713$, Fig. 2], and between TNFi-treated and OA controls [5-year survival 96.6% (89.6–98.9) vs 99.4% (97.7–99.9), $p = 0.123$, Fig. 3].

Reasons for revision

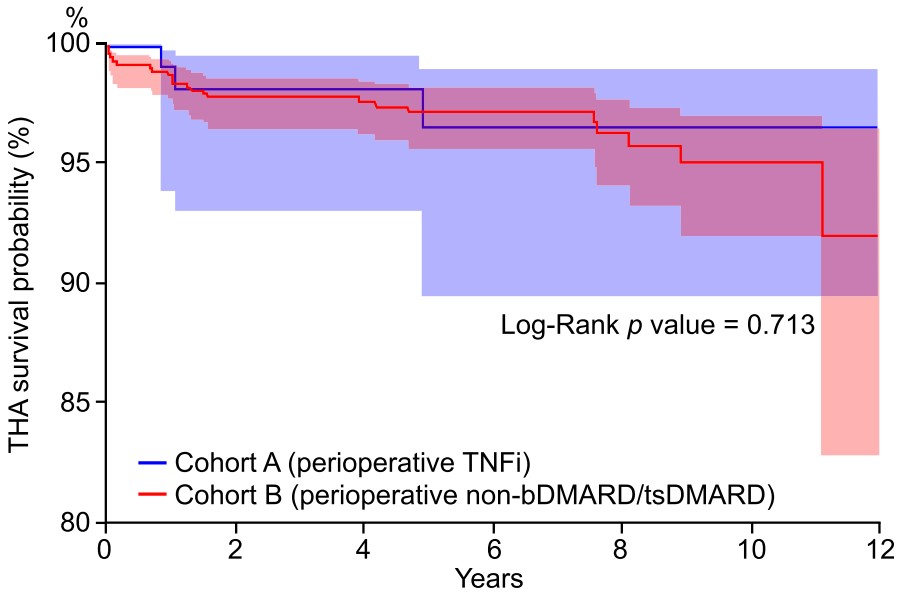
Table 2 reports the distribution of the specific causes for revision surgery of THA implants. Overall, three (2.5%) patients in the TNFi cohort underwent revision surgery, for septic loosening ($n = 1$), periprosthetic fracture ($n = 1$) or dislocation ($n = 1$). In the non-bDMARD/tsDMARD cohort, 26 patients (3%) underwent revision surgery; indications to surgery included septic loosening ($n = 4$), aseptic loosening of the stem ($n = 4$), periprosthetic fracture ($n = 3$), primary instability ($n = 3$) or dislocation ($n = 3$), global aseptic loosening ($n = 2$), periarticular ossification ($n = 1$), aseptic loosening of the cup ($n = 1$) or unknown cause ($n = 5$). Finally, in the primary OA cohort, four patients (0.8%) underwent surgery; indications included early infection ($n = 1$), aseptic loosening of the stem ($n = 1$), aseptic loosening of the cup ($n = 1$) or unknown cause ($n = 1$).

Discussion

The advent of the first bDMARD – namely TNFi – in the late 1990s represented the crucial turning point in the field of rheumatology, revolutionizing the management of arthritic patients by shifting from a broad-immunosuppressive to a pathophysiology-driven treatment paradigm. After more than two decades of widespread use worldwide, evidence from clinical trials [29] and *ad-hoc* registries [30] clearly confirmed the overall effectiveness and safety of these molecules. Despite the availability of these novel therapeutics, a significant proportion of patients with arthritis undergoes joint replacement surgery, and the consequences of background immune-modulating treatment on the outcomes of arthroplasty has not been adequately clarified yet.

Regional and national registries allow us to determine the consequences of the long-term pharmacological treatment on the survival of THA implants. In a study based on the nationwide Danish healthcare register from 1996 to 2011, Cordtz et al. [31] observed that the rate of THA failure requiring surgical revision is increased in patients with RA compared to the general population. A more recent study based on surgeries performed from 2000 to 2014 showed that patients with RA undergoing THA or TKA are at increased risk of death and periprosthetic joint infection compared with patients affected by OA [32]. Biological DMARDs treatment in this patients' population was not associated with a significantly increased risk of prosthetic joint infection or death; conversely, mortality in RA patients was associated with the use of glucocorticoids and with higher disease activity. Despite this, data from our study did not confirm a significantly increased risk of complications requiring revision surgery in inflammatory arthritis patients compared to those affected by OA.

A meta-analysis [18] investigating the perioperative management of TNFi, examined the impact of pre-operative exposure to TNFi on



% Survival (95% confidence interval)

	1Y	3Y	5Y	7Y	10Y
Cohort A (perioperative TNFi) n=121	98.2 (93.0-99.5)	98.2 (93.0-99.5)	96.6 (89.6-98.9)	96.6 (89.6-98.9)	96.6 (89.6-98.9)
Implants exposed at risk	107	81	60	40	13
Cohort B (perioperative non bDMARD/tsDMARD) n=870	98.3 (97.2-99.0)	97.8 (96.5-98.6)	97.1 (95.6-98.2)	97.1 (95.6-98.2)	95.1 (92.1-97.0)
Implants exposed at risk	768	575	409	254	78

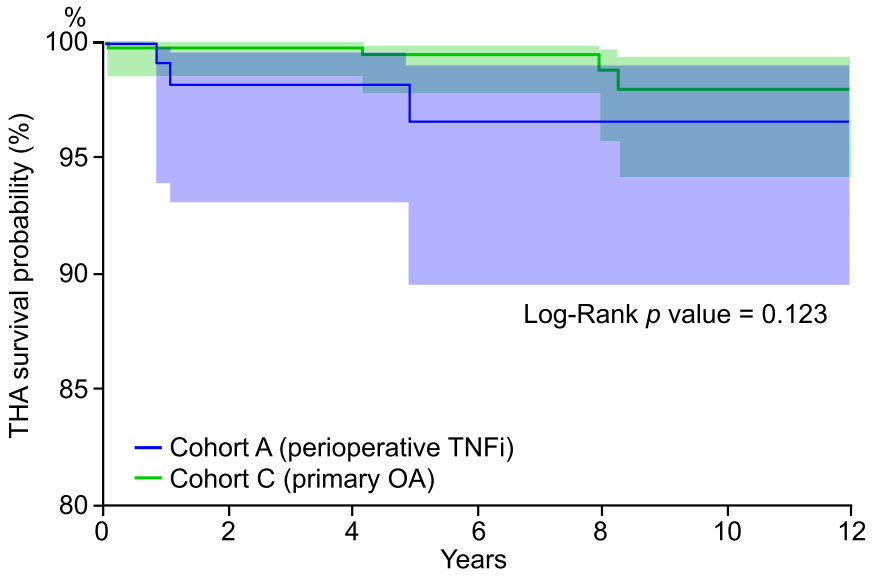
Fig. 2. Survival rates of THA implants for perioperative TNFi recipients VS non-bDMARD/tsDMARD recipients. bDMARD, biologic disease modifying antirheumatic drug; THA, total hip arthroplasty; TNFi, TNF inhibitors; tsDMARD, targeted-synthetic disease modifying antirheumatic drug.

surgical site infection (SSI), and provided useful comparative information. Pooled data analysis suggested an increased risk of SSI for RA patients undergoing elective arthroplasty when exposed to pre-operative TNFi; this finding supports the American College of Rheumatology recommendations to withhold TNFi prior to elective surgery [33]. Despite the retrospective study designs and the heterogeneity due to the different elective orthopedic procedures included, the pooled data reported in the study of Goodman et al. [18] suggest that pre-operative exposure to TNFi (within 3 months of surgery) is associated with a higher risk of SSI for both THA and TKA.

Although these data support withholding TNFi prior to elective orthopedic surgery, their results must be considered in the presence of possible limitations. Misclassification of RA cases in large hospital databases is a recognized problem [34]. Moreover, only the studies conducted by Bongartz et al. [15], den Broader et al. [35], Giles et al. [19], Kawakami [36] and Momohara et al. [37] specify that patients met ACR 1987 criteria for RA diagnosis, while Galloway et al. [8], Johnson et al. [17] and Ruyssen-Witrand et al. [38] used an algorithm that included use of DMARDs to indirectly diagnose RA that may lead to a selection bias towards more severe cases. Other studies [39–41] did not describe the specific RA diagnostic criteria. Furthermore, only six studies assessed the SSI according to the Center for Disease Control (CDC) definition. Both SSIs and deep joint infection were analysed because superficial SSI is highly associated with deep tissue infection [42], and higher overall rates were seen for the TNFi treated group. The significant discrepancy in infection rates could also reflect changes in case definition, with Galloway et al. [8] reporting a 1% rate of septic arthritis against a 12% rate combining both superficial and deep infections in the study by Ruyssen-Witrand et al. [38]. Johnson et al. [17] evaluated 268 RA patients who underwent TKA and examined perioperative usage and risks of TNFi. Overall, 7(3%) SSIs occurred, with 1(0.4%) profound SSI. Three infections occurred among 92 TNFi-treated patients (3.26%) compared to three infections among 143 non-TNFi-treated patients (2.10%), which was not statistically significant ($P = 0.68$).

Another issue is the absence of meticulously documented drugs usage and suspension dates. Patients identified as TNFi-treated may not have taken their medication, resulting in cross-contamination. Moreover, patients with SSI may have been treated elsewhere, resulting in missing data. Furthermore, only few studies [35,40] performed multivariate analysis to account for the effect of confounders and used propensity scores to further attempt to correct these potential sources of bias. Finally, the length of follow-up differed throughout the included studies, which might introduce bias because infections following surgery could be undetected in studies with shorter follow-up periods [19,39] or, conversely, they might include infections that were unrelated to arthroplasty surgery.

Exploiting a large register of arthroplasty started more than 30 years ago, we aimed at contributing to the knowledge on the long-term effects of TNFi on THA revisions in patients with inflammatory arthritis. According to our data, treatment with TNFi does not affect the risk of revision surgery when compared to a similar cohort of arthritis patients not receiving bDMARD or tsDMARD, and even to a propensity score-matched cohort of patients undergoing arthroplasty for primary OA. It is worth noting that, in contrast with previous studies focusing mainly



% Survival (95% confidence interval)

	1Y	3Y	5Y	7Y	10Y
Cohort A (perioperative TNFi) n=121	98.2 (93.0-99.5)	98.2 (93.0-99.5)	96.6 (89.6-98.9)	96.6 (89.6-98.9)	96.6 (89.6-98.9)
Implants exposed at risk	107	81	60	40	13
Cohort C (primary OA) n=473	99.8 (98.5-100.0)	99.8 (98.5-100.0)	99.4 (97.7-99.9)	99.4 (97.7-99.9)	98.0 (94.1-99.3)
Implants exposed at risk	427	342	250	170	53

Fig. 3. Survival rates of THA implants for perioperative TNFi recipients VS primary OA controls. OA, osteoarthritis; THA, total hip arthroplasty; TNFi, TNF inhibitors.

Table 2
Specific causes of revision surgery.

	Cohort A: Perioperative TNFi (n = 121)	Cohort B: Perioperative non-bDMARD/tsDMARD (n = 870)	Cohort C: Primary OA (n = 473)
Septic loosening, n (%)	1 (0.8)	4 (0.5)	–
Early infection, n (%)	–	–	1 (0.2)
Aseptic loosening of the stem, n (%)	–	4 (0.5)	1 (0.2)
Periprosthetic fracture, n (%)	1 (0.8)	3 (0.3)	–
Primary instability, n (%)	–	3 (0.3)	–
Dislocation, n (%)	1 (0.8)	3 (0.3)	–
Global aseptic loosening, n (%)	–	2 (0.2)	–
Ossification, n (%)	–	1 (0.1)	–
Aseptic loosening of the cup, n (%)	–	1 (0.1)	1 (0.2)
Unknown, n (%)	–	5 (0.6)	1 (0.2)
Total, n (%)	3 (2.5)	26 (3.0)	4 (0.8)

Legend: bDMARD, biologic disease-modifying antirheumatic drugs; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; OA, osteoarthritis; TNFi, TNF inhibitors; tsDMARD, targeted synthetic disease-modifying antirheumatic drugs.

on pre-operative bDMARDs recipients, we decided to adopt more stringent criteria for defining perioperative TNFi use including only those with proven pre-operative and post-operative prescription of TNFi. Although reducing the study sample, this approach was able to catch a broader spectrum of potential consequences of perioperative TNFi exposure on THA outcomes including those more probably associated with preoperative exposure (e.g., infectious risk) and those more probably associated with post-implant exposure (e.g., effects of TNF inhibition on bone integration). On the other hand, a potential limitation of our inclusion strategy may be the inability to catch those patients experiencing early complications (e.g., early infection) requiring prolonged discontinuation of the TNFi after surgery: however, further analysis of our data, including careful review of clinical records, revealed no additional safety signals in patients exposed to TNFi preoperatively but not receiving TNFi following surgery.

Further, when comparing the characteristics of the study cohorts, mean age at implant was lower in patients belonging to the perioperative TNFi group, probably reflecting a more aggressive disease phenotype; this finding, on the light of the overall results of the study, may even emphasize the net safety of TNFi treatment on THA survival.

Interestingly, no failures for aseptic loosening were observed in the TNFi group at follow-up. Despite the potentially underpowered patient's cohort, this finding could deserve further studies since aseptic loosening is considered among the most common causes of surgical revision after arthroplasty surgery . Osteolysis, which characterizes this complication, is believed to result from a sustained chronic inflammatory response initiated by particulate debris at the implant-bone interface [21], an event that can be further stimulated by uncontrolled disease activity in arthritis patients [43] in which TNF plays a crucial role [44]. Indeed, TNF takes part in the fine tuning of bone homeostasis; robust in vitro and in vivo evidence demonstrated its role as a promoter of osteoclastogenesis and inhibitor of osteoblastogenesis [45]; this mechanism can sum up with the systemic anti-inflammatory effects resulting in a net reduction of arthritis-associated bone loss [46].

In the current study, the use of perioperative TNFi was not associated to an increase in the risk of revision for infections of THA implants compared to bDMARD/tsDMARD. Our findings are in contrast with those of Momohara et al. [37], that retrospectively identified 81 THA and 339 TKA performed over a 5-year period on their RA patient's cohort. They found 10 infections (1 deep SSI) in 44 biologic DMARD patients' group and 17 on 372 infections (2 deep SSI) in the non-bDMARD group. According to their findings, the use of biologic DMARDs (OR 5.69; 95% CI 2.07, 15.62; $p = 0.0007$) and the duration of RA (OR 1.09; 95% CI 1.04, 1.14; $p = 0.0003$) were significant risk factors for SSI in a multivariate regression analysis. Conversely, our data agree with the findings of Bongartz et al. [15] that did not find differences when analysing the risk of postoperative SSI in 462 RA patients who had THA or TKA, that were matched to an OA cohort based on age, procedure and date of surgery; moreover, no role of the discontinuation of the administration of TNFi was observed in terms of increase of risk of SSI.

Despite contributing novel data regarding the long-term safety of TNFi on the survival of THA in inflammatory arthritis patients, some limitations of our study should be acknowledged. First, our methodological approach to cohorts' definition was based on the interrogation of administrative databases of diseases and prescriptions. Although the sensitivity of those instruments is assumed to be high, they lack clinical information (e.g., disease activity scores, C-reactive protein, autoantibody status). However, comparison of available surrogate data of disease activity at the time of surgery (e.g., concurrent treatment with glucocorticoids) does not suggest mayor differences in the two cohorts. Second, the mixed RA, PsA and AS cohort included in our study may not allow to catch differential effects of TNFi on THA outcomes, as these diseases, although they all benefit from treatment with TNFi, have different immunological background and divergent consequences on bone metabolism.

Third, we were unable to ascertain the actual rate and length of perioperative discontinuation of TNFi, although internal guidelines at the Authors' Institution (developed by shared consensus among orthopedic surgeons, anaesthesiologists, and rheumatologists) require that any DMARD should be withdrawn for at two half-lives before elective THA and resumed after 7–14 days from surgical wound healing. Fourth, on the overall population, we found an unexpectedly low percentage of inflammatory arthritis patients treated with bDMARD/tsDMARD (371/1241, 29.9%). Although a clear explanation cannot be provided on the basis of our data, several factors may be hypothesized to contribute to this finding. All the patients were recruited in a primarily orthopedics setting: although the established diagnosis of arthritis extrapolated from the co-payment exemption register, a proportion of our patients may have received this diagnosis many years earlier and the disease may have been quiescent or in low activity in the years preceding and following surgery. In addition, mean age at the time of surgery of the non-bDMARD/tsDMARD cohort was higher compared to that reported in other rheumatological bDMARD registries [47], with 48.2% of the patients over 70 years old. When treating such older patients, the rheumatologist may be more likely to favor non-immunosuppressive therapy over bDMARDs/tsDMARDs, considering each patient's unique cost-benefit profile. Additionally, 33% of patients in the non-bDMARD/tsDMARD cohort had PsA or AS, conditions for which alternative treatments (e.g., NSAIDs, intra-articular steroids, or physical therapy) can more frequently be sufficient to provide a good control of disease activity and in which therapeutic options beyond TNFi were limited during the study period. Finally, our strategy for the identification of treatment is based on actual medication pick up (a surrogate measure of treatment adherence) and is possible to anticipate a proportion of non-adherence to prescription. Poor adherence, indeed, has been reported in more than 30% of patients with inflammatory arthritis [48]. The relevant relative abundance of TNFi (87.6% of all bDMARD/tsDMARD prescriptions) over other bDMARD/tsDMARD, on the other hand, may be related to the mixed study cohort (including RA, PsA and AS), the earlier approval of TNFi, and the pharmacoeconomic implications of the advent on the market of TNFi biosimilars.

Finally, a priori power calculation was not performed as the RIPO registry entire population was taken into account. On the other hand, several articles support the notion that post-hoc power calculations are never appropriate, as it is already known with certainty whether or not a statistically significant finding has occurred [24–26]. With reference to our study, it has been demonstrated that if a nonsignificant finding is obtained, power will always be low to detect the observed effect size, as observed power is directly related to the obtained p value, with the former providing no additional information than the latter [24–26].

In conclusion, our data, despite the above-mentioned limitations, support the long-term safety of perioperative TNFi on a major hard outcome of THA in patients with inflammatory arthritis. TNFi arthritic patients can safely undergo THA surgery without an increased risk of periprosthetic joint infection compared to those undergoing non-bDMARD/tsDMARD therapy. Prospective studies aimed at the analysis of the bone-implant interface are required to outline the role of TNFi on the prevention of periprosthetic bone loss and peri-implant osteolysis.

Declaration of Competing Interest

The authors have no conflict of interest to declare for the present study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152201.

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