Advanced treatment of ulcerative colitis using an Italian healthcare administrative database: drug utilization patterns, healthcare resource use and costs: The MICHELANGELO study

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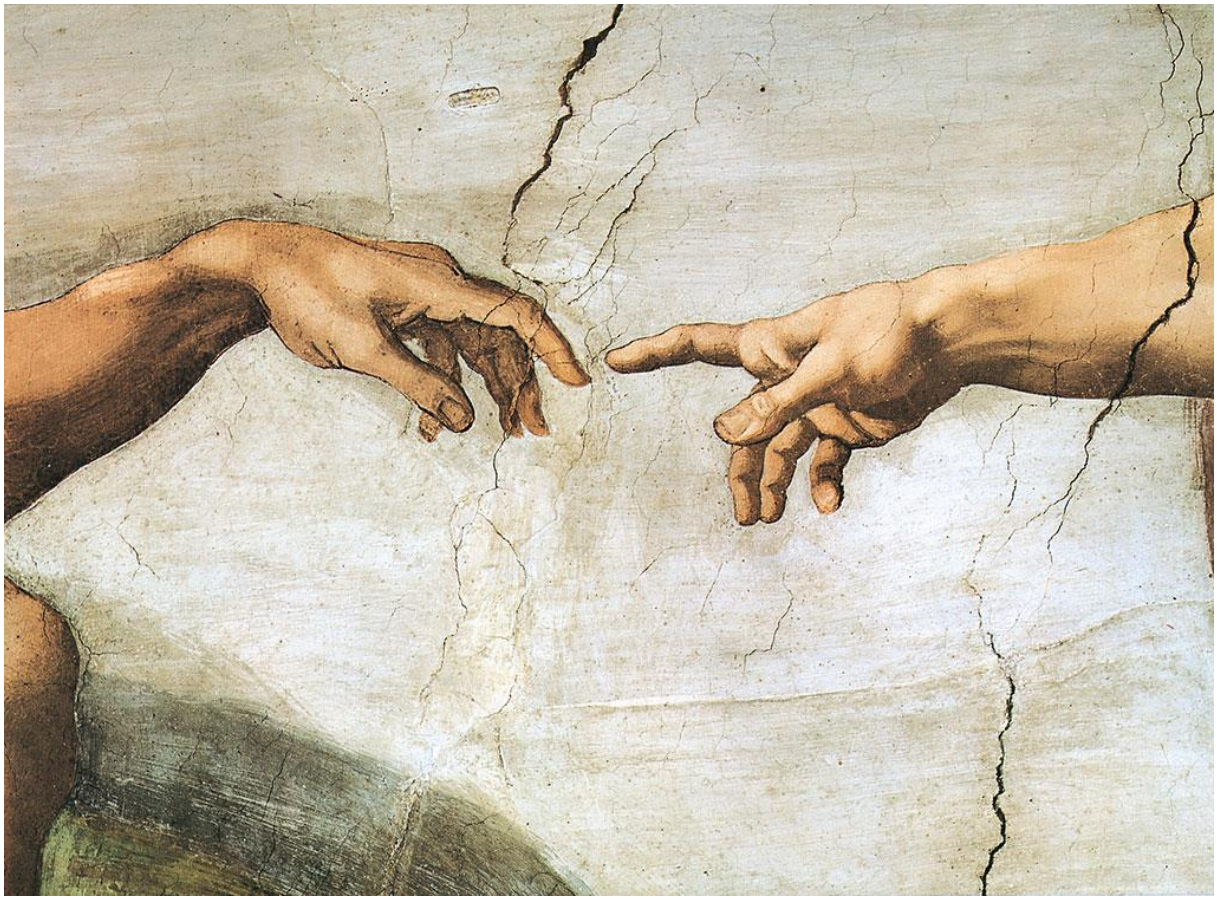
Final Report



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1 Background

Ulcerative colitis is a chronic inflammatory disease treated initially with several anti-inflammatory and immunomodulatory drugs such as 5-aminosalicylates, sulfasalazine, systemic or topical steroids, immunosuppressants (azathioprine, mercaptopurine and cyclosporine), and subsequently with advanced therapies that includes biological drugs like anti-tumor necrosis factor (anti-TNF) agents (infliximab, adalimumab and golimumab), anti-adhesion molecules (vedolizumab) and more recently with JAK inhibitors (tofacitinib)[1]. Treatment failure may occur in about 30% of patients receiving their first treatment (primary non responders), while 10-20% may lose response after an initial disease improvement (secondary non responders). Therefore, switching is a common occurrence.[2] More than 15% of patients will require surgical intervention (proctocolectomy) for colonic high-grade dysplasia/cancer, complications or refractoriness to medical therapy[3]. For these reasons, new therapeutic opportunities for UC are highly desiderable[2]. In this scenario, drug utilization studies using healthcare administrative databases may provide important information for the optimization of care.

2 Advanced treatments for ulcerative colitis

2.1 Adalimumab

Adalimumab is a recombinant "fully human" monoclonal antibody (IgG) targeting the TNF. This drug obtained its first European marketing authorization for rheumatologic disorders in late 2003. Only nine years later, on April 4th, 2012, the European Medicine Agency (EMA) authorized its use in ulcerative colitis (UC), based on results of a placebo-controlled trial showing improvements in bowel inflammation scores and hospitalization rates. In particular, a reduction in all causes and UC-related hospitalizations was observed in patients receiving adalimumab (0.18 and 0.12 per patient year, respectively) compared with placebo (0.26 and 0.22 per patient year, respectively). Some years later, the EMA approved the possibility of increasing adalimumab dose from 40 to 80 mg/week in patients experiencing a disease flare.[4] In 2017, the first biosimilar was authorized and to date, up to 13 adalimumab-biosimilars were available in Europe. [5] In Italy, the Agenzia Italiana Farmaco (AIFA) authorized adalimumab in UC on April 29th, 2014 [6] and defined the related reimbursement class in 2016. [7]

A cohort study analysing retrospectively data of adalimumab use from Maccabi Healthcare Services (Israel), from 2008 to 2013, identified 1339 adalimumab with 119 being UC patients. At baseline, drugs most frequently reported concomitantly with adalimumab were prednisone (31 patients) and azathioprine (23 patients). About 50% of UC patients had at least one hospitalization in the look back and accessed primary care visits more frequently than patients using adalimumab for other indications. In the first 6 months of follow up 67 patients with UC discontinued adalimumab, 18.4% of patients used steroids and 10.9% mercaptopurine. UC patients with medication possession rate ≥ 80% were about 85%. The median time to discontinuation of adalimumab (defined as ≥180-day gap in days of supply) was significantly shorter for UC patients compared with other indications. (Hazard Ratio 1.32 (95% CI 1.02–1.71) [8]. Another real world study compared patterns of use of UC drugs analysing data from the 2017 Adelphi Inflammatory Bowel-Disease Specific Programme (IBD- DSP) for US vs EU5 (France, Germany, Italy, Spain, and the United Kingdom). Among 411 US patients, 37 used adalimumab with or without concomitant immunosuppressant for moderate-to-severe UC as first line, 57 as second line, 37 as third and 9 as fourth line treatment. In the EU5, the distribution of patients using adalimumab for moderate-to-severe UC was 104 as first line, 73 as second line, 54 as third, and 30 as fourth [9]. A retrospective study, performed on data recorded in the IBM MarketScan Research Databases of US, investigated UC-related hospitalization outcomes during 12 months of follow up in UC patients naïve to immunosuppressant or biologic therapy. Out of 1291 naïve adalimumab patients, 166 (12.9%) had at least one record of hospitalization, with a mean 1.61 (standard deviation, SD 1.05) hospitalization and a cumulative length of stay of 8.39 days (SD 9.46) [10]. Perera et al., 2018 in a retrospective cohort study assessing healthcare resource utilization in UC patients initiating biologics, analysed data extracted from a US administrative health insurance claims database and observed patients for 12 (group 1) and 24 mounths (group 2) after the index date, defined by the first biologic prescription. Overall, 4864 and 2692 patients were included in the group 1 and 2, respectively and 1911 and 908 initiated with adalimumab. In the group 1, 616 patients started biologic treatment with adalimumab and received this drug for 1 year of follow-up (as-treated population). Among these, 50 (8.12%) patients had a hospitalization, with mean of 0.10 (SD 0.37) hospitalizations per patient, 133 (21.59%) adalimumab users had an Emergency Department (ED) visit, with mean 0.28 (SD 0.63) ED visits per patient, and 613 (99.51%) users had at least an outpatient visit, with mean 15.35 (SD 12.16) outpatient visits per patient [11].

2.2 Infliximab

Infliximab was the first monoclonal antibody to be approved for the treatment of UC. The European Medicines Agency (EMA) issued the marketing authorisation for infliximab throughout the European Union in August 1999[12]. In Italy, the biologic drug was approved in March 2000[13]. Infliximab is effective for the induction of remission of moderately to severely active UC. It is indicated for adult and paediatric patients who have had an inadequate response to conventional therapy including systemic 5-ASA drugs, corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA)[14]. Infliximab can be chosen as an alternative to adalimumab and golimumab. All monoclonal antibodies are recommended as advanced therapy to induce remission in patients who have become non-responders to standard treatment, or to maintain mucosal healing and remission[14]. When infliximab is used as induction therapy, guidelines recommended the concomitant treatment with a thiopurine. Evidence from observational studies and real-world data is essential to investigate both drug-utilization and the associated clinical outcomes deriving from infliximab usage in clinical practice. Recently, the management of moderately to severely active UC in real-world clinical practice across United States (US) and some European (EU) countries has been examined through the analysis of data collected throughout the 2017 Adelphi Inflammatory Bowel-Disease Specific Programme (IBD- DSP)[9]. The database containing patient chart information was used to extract data on treatment patterns. Overall, 1419 patients with a complete history treatment were evaluated to identify drugs associated with the different treatment lines (359 and 1060 belonging to the US and EU group, respectively). Among them, about 59% (US group) and 47% (EU group) used 5-ASAs and/or steroids in the first line therapy, while immunosuppressants or biologic were mainly used from second to fourth line treatments. In the EU group, the remaining subjects used either an immunosuppressant without a biologic (27.4%) or a biologic (25.5%; mostly infliximab). The frequency of infliximab use was observed to increase in the second line and it was constant for subsequent lines. Infliximab was often administered concomitantly with an immunosuppressive drug.

In a real-world cohort of 3533 UC patients, the pattern of biologic use was assessed together with treatment persistence and switching through the analysis of a US database capturing the continuum of care in all settings including physician outpatient office visits, hospital, pharmacies[15]. Among the included patients, 52.84% began the biologic therapy with infliximab. In addition, patients who started with infliximab generally stayed longer on their initial biologics compared with the other 3 user groups (golimumab, certolizumab and vedolizumab). However, the same

trend was showed for adalimumab. The switching trend showed that infliximab users were most likely to switch to adalimumab, while a low amount of adalimumab initiators switched to infliximab. In accordance, the study by Perera et al.[11] showed that infliximab and adalimumab were the most commonly initiated biologics in patients with UC. This retrospective observational cohort study was conducted on US administrative health insurance claims database and included a large population of UC patients. In particular, the study revealed that the highest proportion of subjects who continued with the same biologic after 1- and 2-years had initiated therapy with infliximab. The analysis of patients who initiated a biologic drug and continued with the same treatment at least for one year showed that after the use of the biologic therapy hospitalization and accesses to ED decreased, while the number of specialist visits remained unchanged. Among the investigated drugs, infliximab was shown to reduce the use of health resources more than the others. These results are in line with previous evidence demonstrating the occurrence of specific events requiring the use of healthcare systems. In a retrospective population-based cohort study performed using health information systems data from an Italian region (Lazio), 469 UC patients who were new users of infliximab were evaluated. Incidence rates (per 100 person-years) of 6.05 for abdominal surgery and 1.14 for hospitalization for infections were observed[16]. However, decrease in gastrointestinal visits, including colonoscopy, surgery and hospitalization was associated with the use of infliximab in a retrospective chart review evaluating resource utilization 12 months before and during infliximab therapy in patients with UC[17].

Overall, the use of health services associated with the use of a drug can be caused by disease-related complications, such as surgery, or other possible ADRs. Over the last years, biosimilar drugs of infliximab were approved and their use in clinical practice has been widely discussed. An Italian study, conducted on data retrieved from the administrative database of Tuscany, showed no relevant changes in the use of healthcare services following the introduction of infliximab-biosimilar to treat patient with chronic diseases included UC [18].

2.3 Golimumab

Golimumab is a drug approved in the European Union and in the United States for the treatment of active rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, polyarticular juvenile idiopathic arthritis and ulcerative colitis. Golimumab is a fully human IgG1 monoclonal antibody that acts by directly binding to the soluble and transmembrane precursor forms of the TNF alpha receptor thus inhibiting the biological activity of this cytokine.

Preclinical studies have shown that golimumab has a higher binding affinity than other TNF alpha inhibitors, such as infliximab or adalimumab, for both soluble and transmembrane TNF alpha. Golimumab is administered by subcutaneous injection because of its high protein stability, which allows it to be prepared as a highly concentrated liquid formulation. This makes possible, after adequate training, the self-administration by patients [19].

In September 2013 Golimumab received the extension of Indication for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6 mercaptopurine (6 MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies [20]. Golimumab is reimbursed by the Italian National Health Service as of January 2015[21]. In May 2013 it also received approval from the FDA to treat adults with moderate to severe ulcerative colitis that is resistant (refractory) to prior treatment or requires continuous steroid therapy. [22]

The FDA and EMA recommend the same initial induction doses for golimumab (starting dose of 200 mg, followed by 100 mg at week 2), whereas maintenance regimens for golimumab differ between Europe and the United States. In Europe, there is a weight-based dosing regimen in which patients weighing less than 80 kg receive 50 mg every 4 weeks and those weighing 80 kg or more receive 100 mg. In contrast, in the United States there is a single dosage of 100 mg every 4 weeks regardless of weight [23] [24].

EMA and FDA approval of Golimumab is based on results from the Program of Ulcerative Colitis Research Studies Using an Investigational Treatment (PURSUIT). Golimumab was evaluated in patients with moderate-to-severe Ulcerative Colitis in 2 phase II/III induction studies, in both intravenous and subcutaneous administration (PURSUIT-IV and PURSUIT-SC, respectively). Already in phase II, enrolment in the PURSUIT-IV study was discontinued because of inefficacy. In PURSUIT-SC, 1064 patients were randomized to receive golimumab SC at induction regimens of 100/50 mg or 200/100 mg or 400/200 mg (week 0/week 2). During phase III, the 200/100 mg and 400/200 mg induction regimens were evaluated and resulted in significant clinical improvements compared with placebo [25]. The phase III PURSUIT - Maintenance (PURSUIT-M) study showed that administration of golimumab as a SC maintenance regimen every 4 weeks in patients with moderate to severe active CU is effective in maintaining clinical response for 1 year. In addition, long-term clinical remission and mucosal healing up to week 54 was shown at the 100 mg dose. The serum concentration of golimumab was associated with maintenance of clinical response[26]. This correlation has been

observed in several other studies, so much so that the appropriateness of using the Therapeutic Drug Monitoring (TDM) of Golimumab in the Treatment of Ulcerative Colitis is under discussion [27].

In recent years, studies have been performed to collect data on the long-term efficacy of golimumab in ulcerative colitis in particular data on continuous real-world clinical response. Bossa et al enrolled 196 patients treated with golimumab in 22 Italian centers. The objective of the study was to evaluate the short- and long-term efficacy and safety of golimumab in daily clinical practice and to identify predictors of response. After 3 months, 130 patients responded (66.3%) and showed significant reductions in disease indices. Regarding long-term response, approximately 39% of patients maintained a sustained response after 12 months of therapy. No significant difference emerged when comparing treatment-naïve patients with patients who had previously failed one anti-TNF-alpha treatment but treatment-naïve patients responded better to golimumab treatment than patients who had failed two treatments with anti-TNF-alpha monoclonal antibodies [28].

In Italy, to ensure the appropriateness of prescribing, the Agenzia Italiana del Farmaco (AIFA) has established a computerized database system for several drugs, including golimumab, accessible to physicians and mandatory to finalize the prescription both at the beginning and during maintenance treatment. Pugliese et. al used this database to conduct an observational study in which consecutive patients who started golimumab therapy in 29 Italian centers were enrolled. This study focused on clinical efficacy and long-term safety in 173 patients with moderate to severe active CU treated with golimumab. The median duration of golimumab therapy was 52 weeks. Most patients (60.7%) had extensive colitis and more than half (53.2%) had already been exposed to at least one ant-TNF-α agent. The cumulative probability of maintaining treatment with golimumab was 47.3% and 22.5% at 54 and 108 weeks, respectively. The authors commented that other real-world experience shows approximately 60% persistence at week 54, and this fact may be due to the inability to increase early to 100 mg in patients with a primary nonresponse or partial response during the maintenance phase. In fact, most patients (75.7%) were maintained on golimumab 50 mg because of their weight (<80 kg). Twenty-two (12.7%) patients underwent total colectomy because of failure to respond to therapy after a median time of 28 weeks from the start of treatment with golimumab [29]. Olivera et al. performed a systematic review of 24 observational studies that evaluated the efficacy of golimumab published between January 1, 2014, and May 15, 2018. The authors measured short-term (6-14 weeks) and mid- and long-term (24-54 weeks) clinical response and remission rates. The medium- and long-term clinical response and

remission rates were 60.3% and 39.2%, respectively, confirming that golimumab is an effective therapy for ulcerative colitis in clinical practice [30].

2.4 Vedolizumab

Vedolizumab is a humanized monoclonal antibody (mAb) anti-α4β7, an integrin expressed on lymphocyte B and T surface that interacts with proteins of the intestinal endothelium. The mAb binds selectively the α4β7 blocking gut lymphocyte circulation.[31] The GEMINI studies, composed of 3 phase III trials, led to the marketing authorisation of vedolizumab for the treatment of ulcerative colitis (UC) on May 2014 in USA[32] and in Europe[33]. On the 13th October 2014 vedolizumab was approved in Italy and it is subjected to reimbursement since 2016[34]. Clinical guidelines[14] and the Summary of Product Characteristics (SPC)[35] recommended vedolizumab for UC in naïve patients or for UC refractory patients to conventional or anti-TNFα treatment. The dosage is 300mg intravenously at week 0, 2 and 6 and then every 8 weeks[35]. Vedolizumab was not often used in first line as shown the retrospective study of Chen et al.[15] On a cohort of newly diagnosed UC (3533 patients, 38,63% of the total cohort) only 0,34% started with vedolizumab compared to other biologics as infliximab, adalimumab, certolizumab or golimumab[15]. In clinical practice, patients started vedolizumab were often in treatment with other therapies. As shown Ylisaukko-oja et al.[31], on a cohort of 139 Finnish patients with UC and who respected eligibility criteria, at vedolizumab initiation 60,4% of patients were in treatment with corticosteroids (CS), 50,4% with immunosuppressant (IS), 66,2% with 5-aminosalicylic acid (5-ASA) and only 14 patients (10,1%) had not concomitant drugs. In details, azathioprine and mesalazine are the most commonly used IS and 5-ASA, respectively. Only 7 patients were in treatment with sulfasalazine at baseline. Considering a period of follow up of 6 months a total of 17,3% of IS users and 8,5% of 5-ASA users who persisted on vedolizumab discontinued the conventional therapy at the end of follow up. More interesting was the CS users' cohort: who persisted on vedolizumab for 6 months were steroid free at months 6 (69,8%). This mean that vedolizumab may have a significant CS-sparing effect. This result is clinically relevant because CSs, often use for long time in this setting, are one of the reason of hospital admission for adverse events. However the percentage of CS users persisted on vedolizumab for 6 months was smaller (above 38,3%) compared to non-users. The SPC recommended to discontinued vedolizumab by week 10 if therapeutic benefit is not observed[33]. The retrospective study of Ylisaukko-oja et al.[31], based on data from 2008 to 2015 of the Truven Health MarketScand, reported that more than a half of patients discontinued

their first biologic within 1 year. The Kaplan-Meier Curve of Persistence showed difference statistically significant between the biologics used for the UC. The persistence rate in the first year for vedolizumab was 64,48%, the highest, but the time of follow up is too short to made conclusion. However persistence result is in line with other studies, including the EVOLVE study[36]. Although the cohort of vedolizumab users was small, no one switched to other biologics during the study period[31].

The systematic review and meta-analysis of Schreiber et al. focused on some clinical endpoints to evaluate the real word effectiveness and safety of vedolizumab[37]. The study period was from May 2014 to June 2017. They included studies, with real word evidence, on adult population receiving vedolizumab. They included 3216 studies on UC. The primary outcome evaluated was the clinical remission. The clinical remission was achieved in about one-third of patients at week 14 (32%; 95% confidence interval CI 27-39%) and in about a half of patients after 12 months (95% CI 37-56%). Then, they evaluated some secondary outcomes as clinical response, CS-free clinical remission, mucosal healing and endoscopic improvement. More than an half of the patients achieved clinical response rate at week 14 already (56%; 95% CI 50-62%). The rate of mucosal healing, an important IBD therapy goal, ranged from 24 to 55% in UC patients, increasing up to 77% after 12 months from baseline; while the endoscopic improvement, at a median time of 22 weeks, was observed in 76% of patients. Another important goal is the CS-free survival that ranged from 14% (95% CI 6%-32%) to 42% (96% CI 31%-53%) at week 6 and month 12, respectively. In terms of hospitalization the result of a study on Swedish registers, that compares the effectiveness of vedolizumab vs anti-TNF agents in second line, showed that the difference in survival without hospitalization related to IBD, was statistically significant and was lower in vedolizumab group (82% vedolizumab vs 93% anti-TNF; p=0.02)[38]. When the retrospective analysis of Long et al. showed that there were no difference statistically significant in number of UC related hospitalization after 12 months from index period between the 4 biologic treatment cohorts (adalimumab, infliximab, golimumab, vedolizumab).[10]

The safety of vedolizumab in UC cohort was evaluated first in the GEMINI trials but it was confirmed by others as the retrospective study of VICTORTY consortium data.[39] Serious adverse events and infections were reported in 4-6% of patients but not all the adverse events were related to vedolizumab. No one discontinued the mAb.

2.5 Tofacitinib

Tofacitinib, available in Italy since October 2018, is a non-selective inhibitor of the JAK family members (pan-JAKi), with a moderate preferential affinity for JAK3 and JAK1[40]. Tofacitinib was first approved by the U.S. Food and Drug Administration (FDA) in 2012 for RA patients, while the European Medicinal Agency (EMA) granted the marketing authorization for tofacitinib to treat adults with RA on March 2017. In 2018, this indication was extended to adults with psoriatic arthritis (PsA) or severe ulcerative colitis (UC)[41]. Tofacitinib was authorized for UC in Italy in 2019[42] and the related reimbursement class was assigned in 2020[43].

In UC, tofacitinib is administered at the dosage of 10mg two times daily for the first 8 weeks and then 5mg twice a day for maintenance[44].

A real world study, performed on data from February 2017 to December 2018 by including French UC patients refractory to anti-TNF and vedolizumab, evaluated time free from colectomy, tofacitinib discontinuation and steroid-free clinical remission at weeks 14, 24 and 48. Among 38 tofacitinib users, the mean age was 41 (standard deviation, SD, 28–52) and had a duration of disease of 7 years as median (IQR 5–11.8). All the included patients had previous treatment with TNF antagonist and vedolizumab, while 4 (10.5%) with ustekinumab and 1 (2.6%) with cyclosporine. Out of tofacitinib users, 77% [95% confidence interval (95%CI): 59.3–87.9] had no event of colectomy at week 24 and 70% (95%CI: 50.9–82.8) at week 48. As regard discontinuation, 70% (95%CI: 52.6–82.3) of patients continued tofacitinib at week 24 and 58.8% at 48 week [45]. Another retrospective cohort study, carried out on four UK centers, investigating 134 UC patients naïve to tofacitinib between 1 October 2018 and 4 October 2019 confirmed the trend of patients free from discontinuation at 24 and 48 weeks of follow-up. When safety profile was assessed, events as hospitalisations, surgery and serious adverse reactions were 8 (6%), 5 (4%), 15 (11%), respectively [46]. Chiorean et al, 2020 provided a description of tofacitinib use in US by using Optum Research Database and including UC patients with the first tofacitinib prescription between May 2018 and July 2019. Adherence was calculated by proportion of days covered (PDC) in 6 months of observation period. Overall, 182 patients were analysed and all of them had a previous prescription of biologic drugs. Out of patients with only one prior biologic, 82.6% had used anti TNF drugs. Mean adherence to tofacinitib was 0.74 [47]. A multicentre retrospective real world study on German patients initiating

tofacinib from August 2018 to March 2020 for UC included 38 drug users and observed them for a median time of 4 months (range 0–18 months) in the follow up and for 12 months in the period before the cohort entry. Among these, 8 (21.1%) patients had a history of hospitalization, 6 (15.8%) had UC-related hospitalizations at baseline, 34 (89.5%) users had a previous prescription of anti-TNF, 26 (68.4%) of anti-integrin drugs, 30 (78.9%) of immunomodulators, 26 (68.4%) of mesalazine/sulfasalazine and 21 (55.3%) of steroids including budesonide. 53% of users continued tofacitinib at week 24. As far as safety is concerned, three patients experienced serious adverse events at week 8 and one of these was associated with hospitalization due to exacerbation of UC. None of patients had serious events including hospitalization between 8 and 24 weeks [48].

3 Objective

In this study, we identified and described new users of advanced therapies for UC (adalimumab, infliximab, golimumab, vedolizumab, tofacitinib) in Tuscany from January 1st 2015 to December 31st, 2019. In particular, we described their utilization in the Regional Healthcare System (RHS) facilities both before and after treatment initiation. Furthermore, we provided also an evaluation of the economic impact of patients using advanced therapies for UC considering the overall costs and cost per patients, costs associated to drugs (both advanced therapies and other drugs), utilization of the Regional Healthcare System (RHS) facilities (i.e. ED admissions, hospitalizations, specialists visits) after treatment initiation considering the perspective of the Regional Health Services.

4 Research questions

1. What was the history of utilization of drugs with possible use in UC (**see table 1**) in new users of any advanced treatments for UC (adalimumab, infliximab, golimumab, vedolizumab, tofacitinib) in Tuscany between January 1st, 2015 to December 31st, 2019?
2. What is the utilization pattern of drugs for UC within one or two years in new users of any advanced treatment for UC in Tuscany between January 1st, 2015 to December 31st, 2019?
3. What was the pattern of Healthcare utilization (Emergency Department access, Hospitalization, access to specialist visits) within one or two years after initiating any advanced treatment for UC in Tuscany?
4. What were the estimated direct health costs per patient/year within one or two years after initiating an advance treatment for UC in Tuscany, overall and stratified by type of cost and year of cohort entry?

Table 1 Drugs of interest

Drug(s)	**ATC code(s)**
Advanced therapies (index drugs)	
Infliximab	L04AB02
Adalimumab	L04AB04
Golimumab	L04AB06
Vedolizumab	L04AA33
Tofacitinb	L04AA29
Other treatments of interests	
Other biologic including Ustekinumab	L04AA* e L04AB*
Antibiotics	A07A* AND J01*
Salicilates	A07EC*
Mesalazine	A07EC02
Azathioprine	L04AX01
Methotrexate	L01BA01 and L04AX03
Ciclosporin	L04AD01
6-mercaptopurine	L01BB02
Corticosteroids for systemic use	H02*
Locally acting corticosteroids	A07EA*
Tacrolimus	L04AD02

5 Methods

5.1 Study design

This is a descriptive, retrospective cohort study.

5.2 Data source

We used data retrieved from administrative healthcare databases of Tuscany. Particularly, the study database was obtained linking records from 4 different administrative repositories: hospital discharge (SDO) (cause of hospitalization [ICD-9 code], date of hospitalization and discharge, cost of hospitalization), emergency department (ED) admission (cause of ED admission [ICD-9 code], date of ED admission and discharge), of drug dispensations (drugs [ATC codes], gender, birth date, dates of drug dispensation, drug doses, drug costs), and specialist encounters (gastroenetrologic visits, date of gastroenetrologic visits, cost of visits)[49]. Data were linked among databases using an anonymous unique patient code.

5.3 Definition of cohorts

In order to answer to the above research questions (RQ), we created 5 different study cohorts (one for each drug of interest). For each cohort of drug users, we identified two different cohorts based on the available follow-up period: the first cohort included patients with at least one year of follow-up and the second cohort patients with at least two years of follow-up. The expected final number of analyzed cohort was 10. However, since tofacitinib was authorized in UC in Italy only in 2019, we did not identify any patient that could have assumed tofacitinib for UC. Therefore, the final number of analyzed cohorts is 8. Cohorts' definition is described in detail below.

5.3.1 Adalimumab cohort

We included new users of an adalimumab between January 1st, 2015 and December 31st, 2019 with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward (code: 058) in the year before the index date. Index date was the date of the first supply. We defined new user

each subject without supply of adalimumab in the look-back period (5 years before the index date). Patients were followed up for one or two years after the index date. Follow-up was defined from the index date to death or one/two years after the index date (last follow-up date was December 31st, 2020). We excluded patients with less than 5 years of records in the look back period and those with less than 1 year of follow-up. We also excluded patients receiving more than one of the advanced therapy at the index date and patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis psoriasis, multiple sclerosis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis (ICD-9 696.0), hidradenitis suppurativa / acne inversa, uveitis intermedia, uveitis posterior und panuveitis at any time during in the look-back period. These criteria identified only patients with prompt record (clinically relevant conditions). Patients aged ≤ 18 at index date were also excluded. To exclude patients that could have taken adalimumab for other indications we excluded patients with record of use of oral budesonide in the 5 years before cohort entry (oral budesonide is indicated only as initial treatment for Crohn Disease) and patients with records of visits in rheumatology ward or dermatology ward in the 1 year before cohort entry.

5.3.2 Infiximab cohort

We included new users of infliximab between January 1st, 2015 and December 31st, 2019 with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward in the year before the index date. Index date was defined by the date of the first supply. We defined new user each subject without supply of infliximab in the look-back period (5 years before the index date). Patients were followed up for one or two years after the index date. Follow-up was defined from the index date to death or one/two years after the index date (last follow-up date was December 31st, 2020). We excluded patients with less than 5 years of records in the look back period and those with less than 1 year of follow-up. We also excluded patients receiving more than one of the advanced therapy at the index date and patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, hidradenitis suppurativa / acne inversa, uveitis intermedia, uveitis posterior und panuveitis at any time during in the look-back period. This criterion identified only patients with prompt record (clinically relevant conditions). Patients aged ≤ 18 at index date were also excluded. To exclude patients that could have taken infliximab for other indications we excluded patients with record of use of oral budesonide in the 5 years before cohort entry

(oral budesonide is indicated only as initial treatment for Crohn Disease) and patients with records of visits in rheumatology ward or dermatology ward in the 1 years before cohort entry.

5.3.3 Golimumab cohort

We included new users of golimumab between January 1st, 2015 and December 31st, 2019 with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward in the year before the index date. Index date was defined by the date of the first supply. We defined new user each subject without supply of golimumab in the look-back period (5 years before the index date). Patients were followed up for one or two years after the index date. Follow-up was defined from the index date to death or one/two years after the index date (last follow-up date was December 31st, 2020). We excluded patients with less than 5 years of records in the look back period and those with less than 1 year of follow-up. We also excluded patients receiving more than one of the advanced therapy at the index date and patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, hidradenitis suppurativa / acne inversa, uveitis intermedia, uveitis posterior und panuveitis at any time during in the look-back period. This criterion identified only patients with prompt record (clinically relevant conditions). Patients aged ≤ 18 at index date were also excluded. To exclude patients that could have taken golimumab for other non-gastroenterological indications we excluded patients with records of visits in rheumatology ward or dermatology ward in the 1 year before cohort entry.

5.3.4 Vedolizumab cohort

We included new users of vedolizumab between January 1st, 2015 and December 31st, 2019 with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward in the year before the index date. Index date was defined by the date of the first supply. We defined new user each subject without supply of vedolizumab in the look-back period (5 years before the index date). Patients were followed up for one or two years after the index date. Follow-up was defined from the index date to death or one/two years after the index date (last follow-up date was December 31st, 2020). We excluded patients with less than 5 years

of records in the look back period and those with less than 1 year of follow-up. We also excluded patients receiving more than one of the advanced therapy at the index date and patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, hidradenitis suppurativa / acne inversa, uveitis intermedia, uveitis posterior und panuveitis at any time during in the look-back period. This criterion will identify only patients with prompt record (clinically relevant conditions). Patients aged ≤ 18 at index date were also excluded. To exclude patients that could have taken vedolizumab for Crohn disease we excluded patients with records of use of oral budesonide in the 5 years before cohort entry (oral budesonide is indicated only as initial treatment for Crohn Disease).

5.3.5 Tofacitinib cohort

We included new users of tofacitinib between January 1st, 2015 and December 31st, 2019 with a diagnosis OR a co-payment exemption code for UC in the lookback period or in the follow up OR a visit in a gastroenterology ward in the year before the index date. Index date was defined by the date of the first supply. We defined new users each subject without supply of tofacitinib in the look-back period (5 years before the index date). Patients were followed up for one or two years after the index date. Follow-up was defined from the index date to death or one/two years after the index date (last follow-up date was December 31st, 2020). We excluded patients with less than 5 years of records in the look back period and those with less than 1 year of follow-up. We also excluded patients receiving more than one of the advanced therapy at the index date and patients with a diagnosis or a co-payment exemption code for Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis, axial spondyloarthritis and ankylosing spondylitis, psoriatic arthritis, hidradenitis suppurativa / acne inversa, uveitis intermedia, uveitis posterior und panuveitis at any time during in the look-back period. This criterion identified only patients with prompt record (clinically relevant conditions). Patients aged ≤ 18 at index date were also excluded. To exclude patients that could have taken tofacitinib for other non-gastroenterological indications we excluded patients with records of visits in rheumatology ward or dermatology ward in the 1 year before cohort entry.

5.4 Data analysis

For RQ-1, we calculated the number of patients with at least one-year follow up receiving their first advanced therapy (adalimumab, infliximab, golimumab, vedolizumab, tofacitinib) in the study period (overall and stratified by year, age, gender), and the number of patients with at least one-year follow up with history of dispensation of drug of interest (table 1) before cohort entry. Finally, we have estimated the number of defined daily doses (DDD), and the mean DDD per patient of each drug of interest before cohort entry.

For RQ-2, in each of the 5 cohorts of users (index drugs: tofacitinib, adalimumab, infliximab, golimumab, vedolizumab) we have calculated the number of DDD of the index drug in the one-year and two-year follow up periods, overall and stratified by calendar year of cohort entry. Then, we have estimated the Percentage of Day Covered (PDC) by the index drugs during the one-year and two-year follow-up periods. We have also calculated the number of patients with at least one prescription of an advanced therapy other than the index drug in the one-year and in the two-year follow-up periods and stratification based on the different advanced therapies supplied. We performed a survival analysis to estimate the time free from an advanced therapy different from any index drug in the one-year and the two-year follow-up periods (Kaplan-Mayer). We have calculated the number of patients with at least one prescription of a drug of interest **(table 1)** in the one-year and two-year follow-up periods. We have estimated the number of DDD received for any advanced therapy other than the index drug in the one-year and two-year follow-up periods, overall and stratified by calendar year of cohort entry. Finally, we have calculated the number of DDD received for any drug of interest in the one-year and two-year follow-up periods, overall and stratified by calendar year of cohort entry.

For RQ-3, we calculated the number of access to ED, Hospitalizations and gastroenterological visits for any cause during the one year and the two-year follow up periods for each advanced therapy. We have also estimated the number of patients with at least one access to ED, Hospitalization and gastroenterological specialist visits during the one year and the two-year follow up for each advanced therapy, overall and stratified by gender, age group, and calendar year of cohort entry. In patients with at least one access in ED, hospitalization or gastroenterological visits during the follow up, we have estimated median and mean time to the first record. We have also described the causes of ED admission and hospitalization during the follow-up and their frequency.

For RQ-4, we described for each cohort initiating different advanced therapies, the direct health costs born to the RHS accounting for the size of the study cohort to assess the impact on the regional healthcare budget; median and mean per patient direct costs (overall and according to different costs component related to drugs, ED admissions, hospitalization and gastroenterological visits as recorded in the regional healthcare administrative databases) over one-year and two-year after treatment initiation were also assessed to evaluate per patient costs within the target population. For each cohort, an overview of costs over one-year and two-year according to the year of cohort entry were also provided.

6 Results

After the application of inclusion and exclusion criteria, we have identified two cohorts of new users with at least one-year and two-years of follow-up (respectively) for adalimumab (**Figure 1**); infliximab (**Figure 2**), golimumab (**Figure 3**) and vedolizumab (**Figure 4**). For tofacitinib, there are not patients selected by inclusion and exclusion criteria, because the drug was approved for UC in Italy in late 2019 and no patients have 1 year of follow-up to be included in the cohort.

Figure 1 - ADALIMUMAB COHORTS

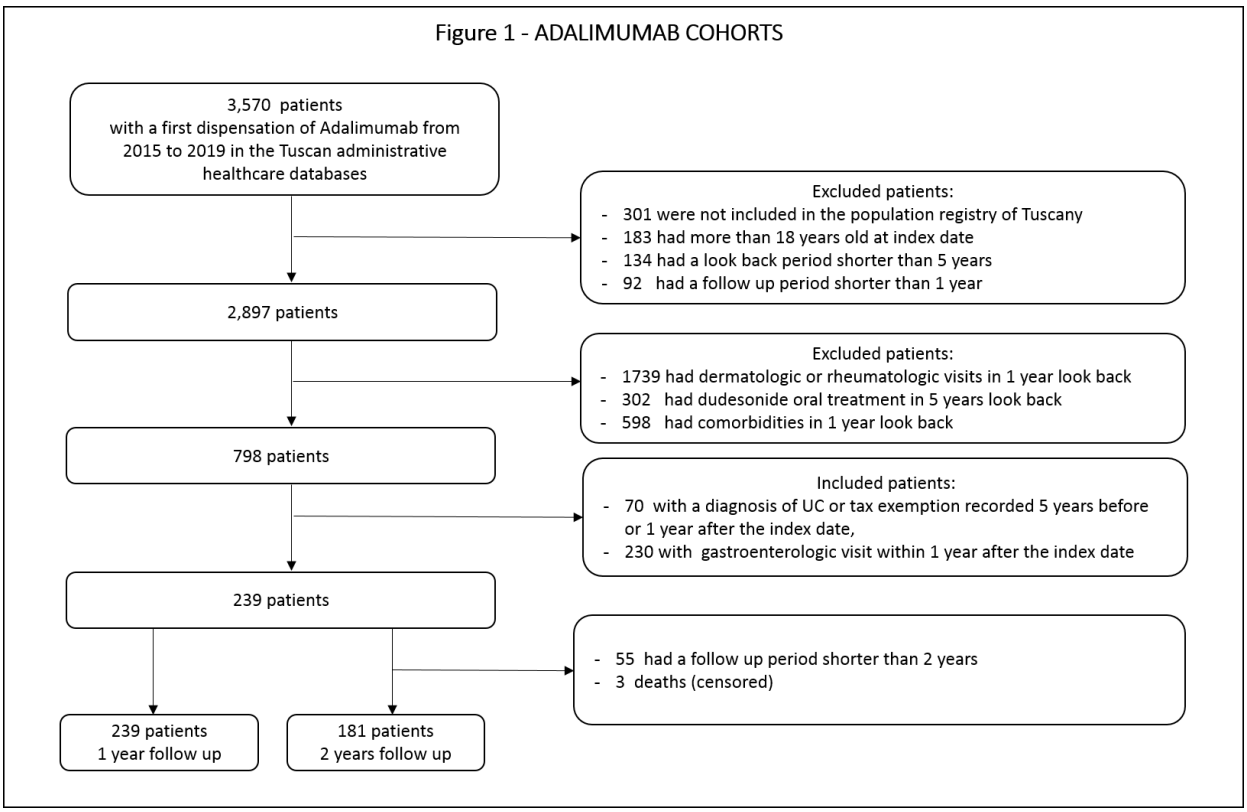


Figure 2 - INFLIXIMAB COHORTS

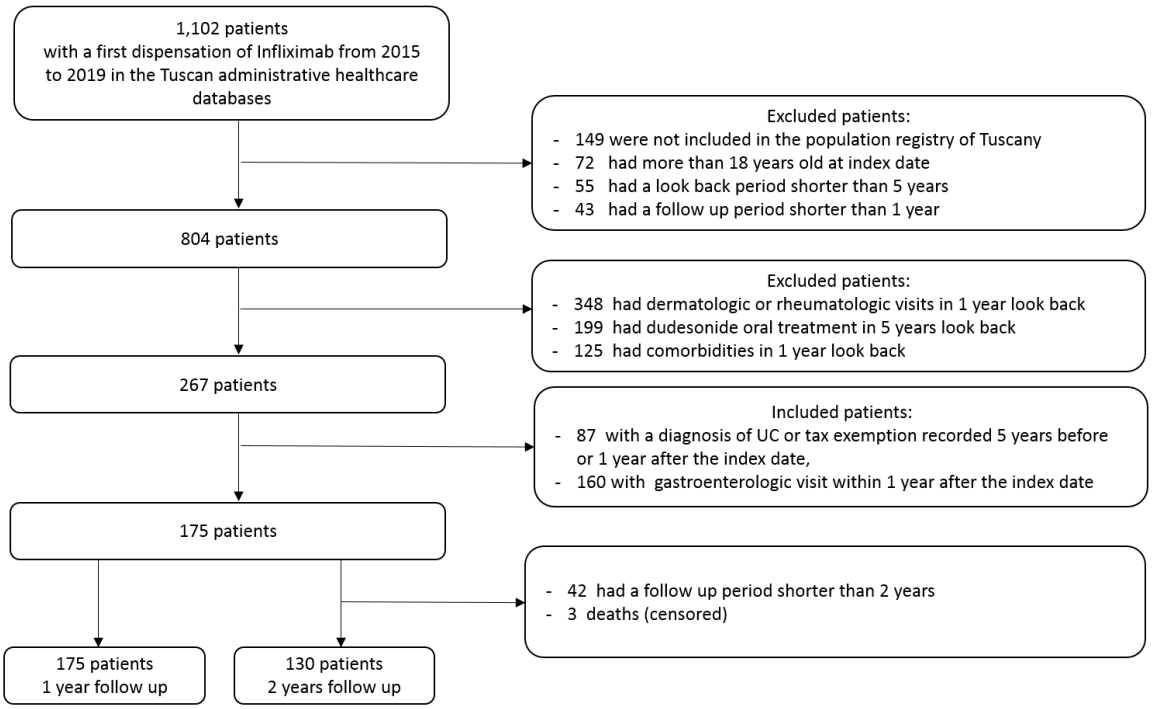


Figure 3 - GOLIMUMAB COHORTS

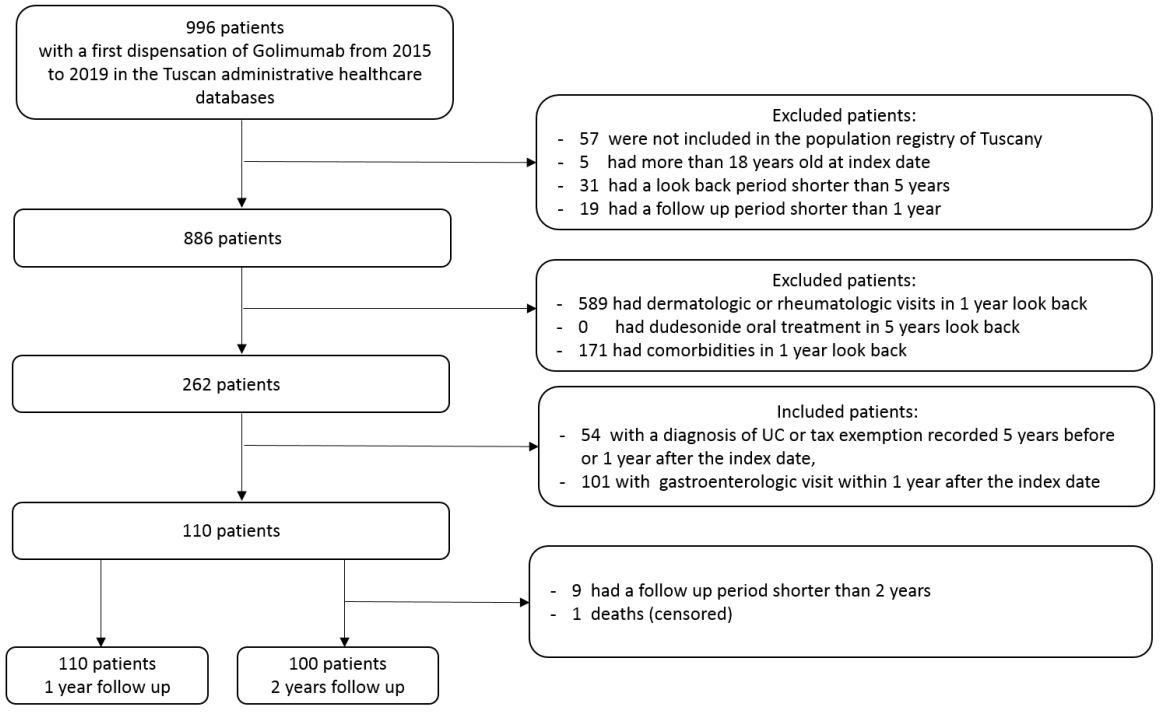
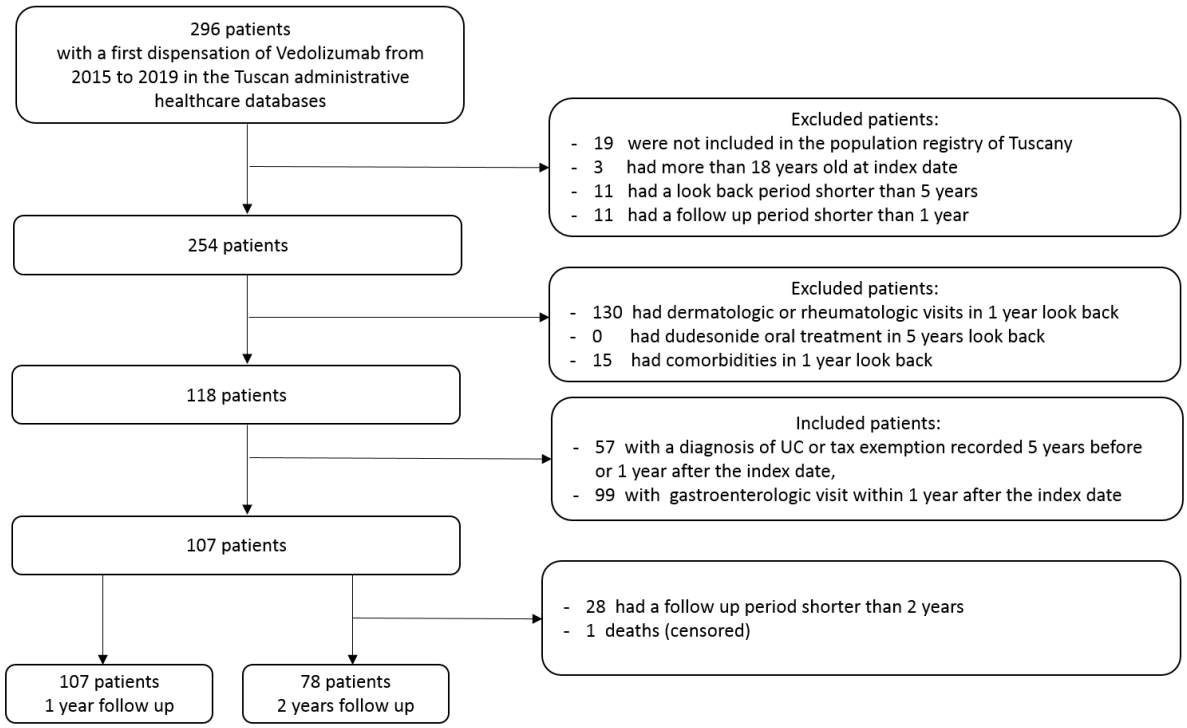


Figure 4 - VEDOLIZUMAB COHORTS



6.1 Research question 1

As showed in **Table 2**, new users were predominantly males with median age ranging from 47 years for infliximab and adalimumab to 52 for vedolizumab. New users of vedolizumab were older than the others even when the median age was considered. This could be due to the most recent authorization of vedolizumab in UC which was most frequently used as a third line treatment, i.e. after non-biologics and the first biologic. A high percentage of patients with a history of at least one hospitalization or ED access was observed for vedolizumab. This likely appeared related to a use of vedolizumab in patients older and with severer disease than those using the other drugs. Notably, vedolizumab is the last authorized drug among the others advanced therapies for UC and it is the only one introduced during the observation period. It is likely that when arrived on the market vedolizumab underwent a somehow selective prescription, a situation typical of new marketed drugs, to specific patients (for instance those resistant to other biologic, those particularly healthy, or particularly frail). This selection could have driven some outcomes. The number of gastroenterological visits was more or less similar for all users in the look-back period.

When we observed the previous use of other therapies, we found that 70% of the patients treated with vedolizumab had already received advanced therapy previously. This confirms its use as an advanced second-line therapy. In all the five cohorts, the patients had previous treatments with first-line drugs frequently used in UC patients, as antibiotics and mesalazine. In particular, a percentage ranging from 73% (adalimumab cohort) to 96% (vedolizumab cohort) had a history of mesalazine use, and a percentage greater than 95% used antibiotics in all cohorts. The use of systemic corticosteroids ranged between 86% (adalimumab) and 96% (vedolizumab). There are no users with previous treatment of tofacitinib (this confirms the exclusion of patients with rheumatologic diseases for which tofacitinib has also indication) and tacrolimus. The number of users who had a biological therapy as first-line treatment (no previous drug of interest) was negligible. It is possible that for these subjects the treatment was not captured by the information flows of the regional health databases because these had purchased the drugs privately or outside the region (**Table 3**). The details of the DDDs used for the drugs of interest and other advanced therapies in the 5 years preceding the index date for each cohort is shown in **table 4**. The use of other immunosuppressant included among drugs of interest is higher in new users of adalimumab compared with other index drugs probably because adalimumab is more frequently used as first ever biologic (see table 3). Indeed, in biologic non-naïve patients that are new users of an advanced therapy the disease was likely controlled in the past five years with a biologic, thus requiring

less supplying of other immunosuppressant drugs. The use of antibiotics seems to be higher in infliximab users compared with other index drugs. This could suggest somehow a selective prescription of this drugs in subjects with history of infections. We are not able to provide a scientific rationale for this choice and this hypothesis should be confirmed in future investigations.

Table 2 – Characteristics of new users of advanced therapy for UC in the year before index date

	Adalimumab	Infliximab	Golimumab	Vedolizumab
Overall, N	239	175	110	107
Sex				
Male, N (%)	131 (55%)	103 (59%)	63 (57%)	61 (57%)
Female, N (%)	108 (45%)	72 (41%)	47 (43%)	46 (43%)
Age in years				
mean (± SD)	47.26 (±16.53)	46.67 (± 16.22)	48.55 (±15.49)	52.7 (±16.45)
median (± IQR)	48 (±26)	48 (±25)	49 (±21.75)	58 (±27)
Hospitalizations				
Patients without events	157 (66%)	72 (41%)	80 (73%)	59 (55%)
Patients with at least one event, N (%)	82 (34%)	103 (59%)	30 (27%)	48 (45%)
Number of events, mean (± SD)	124, 1.51 (±0.82)	165, 1.6 (±1.03)	44, 1.47 (±0.82)	78, 1.62 (±0.98)
ED accesses				
Patients without events	140 (59%)	82 (47%)	69 (63%)	49 (46%)
Patients with at least one event, N (%)	99 (41%)	93 (53%)	41 (37%)	58 (54%)
Number of events, mean (± SD)	151, 1.53 (±0.84)	181, 1.95 (±1.24)	55, 1.34 (±0.73)	105, 1.81 (±1.28)
Gastroenterological specialist visits				
Patients without events	9 (4%)	15 (9%)	9 (8%)	8 (7%)
Patients with at least one event, N (%)	230 (96%)	160 (91%)	101 (92%)	99 (93%)
Number of events, mean (± SD)	1123, 4.88 (±14.54)	844, 5.28 (±10.09)	494, 4.89 (±4.36)	547, 5.53 (±4.08)

SD: standard deviation; IQR: interquartile range, ED: emergency department

Table 3 - History of use (5 years before index date) of drugs in patients receiving advanced therapies for UC

	Adalimumab	Infliximab	Golimumab	Vedolizumab
Overall	239	175	110	107
Use of advance therapy				
No use, N (%)	202 (85%)	122 (70%)	70 (64%)	38 (35%)
Any use, N (%)	37 (15%)	53 (30%)	40 (36%)	69 (65%)
Tofacitinib, N (%)	-	-	-	-
Adalimumab, N (%)	x	42 (79%)	27 (68%)	33 (48%)
Infliximab, N (%)	29 (78%)	x	20 (50%)	48 (70%)
Golimumab, N (%)	9 (24%)	11 (21%)	x	14 (20%)
Vedolizumab, N (%)	-	3 (6%)	2 (6%)	x
Combination of 2 advanced therapies, N (%)	1 (3%)	3 (6%)	7 (18%)	18 (26%)
Combination of 3 advanced therapies, N (%)	-	-	1 (3%)	4 (6%)
Combination of 4 advanced therapies, N (%)	-	-	-	-
Use of other drugs				
No use, N (%)	2 (1%)	2 (1%)	-	-
Any use, N (%)	237 (99%)	173 (99%)	110 (100%)	107 (100%)
Other biologic including Ustekinumab, N (%)	16 (7%)	3 (2%)	5 (5%)	2 (2%)
Antibiotics, N (%)	230 (97%)	165 (95%)	105 (95%)	105 (98%)
Salicilates, N (%)	35 (10%)	16 (9%)	19 (17%)	13 (12%)
Mesalazine, N (%)	172 (73%)	145 (84%)	95 (86%)	103 (96%)
Azathioprine, N (%)	56 (24%)	49 (28%)	46 (42%)	36 (34%)
Methotrexate, N (%)	22 (9%)	6 (3%)	10 (9%)	4 (4%)
Ciclosporin, N (%)	4 (2%)	-	3 (3%)	1 (0%)
6-mercaptopurine, N (%)	16 (7%)	6 (3%)	10 (9%)	9 (8%)
Corticosteroids for systemic use, N (%)	203 (86%)	161 (93%)	101 (92%)	103 (96%)
Locally acting corticosteroid, N (%)	106 (45%)	107 (62%)	85 (77%)	83 (76%)
Tacrolimus, N (%)	-	-	-	-
No use of advanced therapies nor other drugs, N (%)	2 (0%)	2 (1%)	-	-
Use of other drugs but not any advanced therapies, N (%)	200 (84%)	120 (69%)	70 (64%)	38 (35%)
Use of advanced therapies and other drugs, N (%)	37 (16%)	53 (30%)	40 (36%)	69 (65%)

Table 4 - Dispensation of Drugs of interest (5 years before cohort entry) in patients receiving advanced therapies for UC

	Adalimumab		Infliximab		Golimumab		Vedolizumab	
Drugs	Number of users, Total Number of DDD	Mean of DDD per user, (± SD)	Number of users, Total Number of DDD	Mean of DDD per user, (± SD)	Number of users, Total Number of DDD	Mean of DDD per user, (± SD)	Number of users, Total Number of DDD	Mean of DDD per user, (± SD)
Advanced therapies								
Tofacitinib	-	-	-	-	-	-	-	-
Adalimumab	x	x	42, 27752	661 (±477.14)	27, 17269	640 (±508.09)	33, 22621	685 (±718.53)
Infliximab	29, 25547	881 (±730.46)	x	x	20, 15307	765 (±599.12)	48, 39066	814 (±749.81)
Golimumab	9, 6325	703 (±514.03)	11, 4398	400 (±246.21)	x	x	14, 4940	353 (±230.43)
Vedolizumab	-	-	3, 500	167 (±55.56)	2, 944	472 (±353.56)	x	x
Other therapies								
Other biologics	16, 7578	474 (±304.5)	3, 3171	1057 (±824.11)	5, 726	145 (±100.22)	2, 662	331 (±256.33)
Antibiotics	230, 13327	58 (±82.69)	165, 17579	107 (±292.59)	105, 6821	65 (±65.17)	105, 8627	82 (±88.99)
Salicilates	35, 11049	316 (±491.80)	16, 5478	342 (±509.01)	19, 12281	646 (±732.24)	13, 8971	690 (±792.13)
Mesalazine	172, 330480	1921 (±1688.8)	145, 242021	1669 (±1533.51)	95, 228831	2409 (±1600.28)	103, 238959	2320 (±1640.46)
Azathioprine	56, 33434	597 (±522.95)	49, 22034	450 (±486.86)	46, 18400	400 (±539.82)	36, 14534	404 (±470.76)
Methotrexate	22, 5701	259 (±332.93)	6, 1126	188 (±231.55)	10, 2105	211 (±286.53)	4, 1317	329 (±402.33)
Ciclosporin	4, 1296	324 (±320.79)	-	-	3, 384	128 (±134.88)	1, 1410	-
6-mercaptopurine	16, 2992	187 (±183.05)	6, 1075	179 (±244.93)	10, 2500	250 (±233.62)	9, 2333	259 (±236.52)
Corticosteroids for systemic use	203, 73559	362 (±404.97)	161, 68032	423 (±473.37)	101, 45079	446 (±332.92)	103, 54329	527 (±508.82)
Locally acting corticosteroids	106, 26818	253 (±290.76)	107, 30966	289 (±307.63)	85, 28562	336 (±317.31)	83, 28472	343 (±379.19)
Tacrolimus	-	-	-	-	-	-	-	-

6.2 Research question 2

For research question 2, 3 and 4 we used the same cohort used for answering the research question 1. Additionally, we created a cohort of patients with at least two years of follow-up for each drug of interest to explore drug and healthcare resources utilization in a longer period. These cohorts included 181 new users of adalimumab, 130 new users of infliximab, 100 new users of golimumab and 78 new users of vedolizumab.

For subjects with at least one year of follow-up (**table 5**), there was a continuous use of advanced treatments with a mean coverage even exceeding 100% of days of treatment. This could be explained by the clinical practice use of these drugs, for which the induction doses are two or four times higher than the DDD recommended by the World Health Organization. In addition, the use of a higher dose, usually double when compared with DDD, is recommended in the event of disease worsening. The fluctuations in the use of advanced therapies are likely related to regional health policy reasons and particularly to the recommendation following the introduction of biosimilar infliximab and adalimumab in the observed period. This is also documented by previous studies conducted on the same database [18]. In the 2019 cohorts, some effects of the COVID-19 pandemic could also be observed in comparison with 2018. In particular, adalimumab, which can be administered at home, has increased its use (total DDD), while less DDD were consumed for drugs requiring intravenous infusion (infliximab and vedolizumab). We cannot exclude that in some cases, prescribers had preferred home therapies in line with the needs of social distancing imposed by the pandemic. In the cohorts of patients with at least two years of follow-up (**table 6**), no particular differences were observed in the use trends evaluated two years after the index date.

In users with at least one year of follow-up (**table 7**), a percentage ranging between 8% (vedolizumab) and 22% (golimumab) of patients was found to use another advanced therapy within the first year of treatment, thus identifying a switching event. Subjects using adalimumab, golimumab or vedolizumab switched primarily to infliximab, while those taking infliximab switched to vedolizumab. Switching often seems to take place from home therapy to hospitalized intravenous therapy, which might suggest that in

some cases the prescribers tried to ensure patient compliance. In the cohorts with at least two years of follow-up (**table 8**), the trends observed up to one year seem to be maintained.

Figure 5 shows time free from advanced therapy different from any index drug in one-year follow-up and at one year the 90% of users remained in therapy with all the index drugs with the exception of golimumab (80% of patients). This was also confirmed at two-year of follow up except for vedolizumab which remained stable above 90% (**Figure 6**). This difference in persistence in therapy could be explained even by the possible selective prescription described in the paragraph 6.1.

The trends of use of other drugs of interest in the first (**table 9**) and second year (**table 10**) of treatment with all advanced therapies remained fairly in line with data observed in the look-back period. Antibiotics, mesalazine and corticosteroids for systemic use were the most used drugs in new users of advanced therapies for UC.

The DDD provided for each advanced therapy other than the index drug was homogeneous in both the one-year follow-up cohort (**Table 11**) and the two-year follow-up cohort (**Table 12**). The fluctuations are likely associated with the small number of subjects who switched to another advanced therapy in the first or second year from the start of treatment. In this case the regional drug access policies and the introduction of infliximab and adalimumab biosimilars may have had an effect on the consumption of other advanced therapies in each cohort over the years. The consumption of other drugs of interest at one year (**table 13**) and two years (**table 14**) of follow up also showed stable trends over the years. In accordance with UC clinical guidelines, there is a wide concomitant use of mesalazine during the treatment with all the four drugs of interest. A lower percentage of adalimumab new users received mesalazine dispensation during the first year of treatment compared to other index drugs This may be due to the fact the adalimumab is more frequently the first ever biologic. Patients receiving their first ever biologic are expected to achieve a good response than those using second-line biologics (resistant disease) and therefore these may require less frequently immunosuppressant to control the disease. The use of antibiotics remained high in all new users of index drugs thus confirming that this cohort is particularly subjected to infections. Again, this large use of antibiotics

maybe the results of chronic use of immunosuppressant and corticosteroids before and after the index date. There are not great fluctuations of the use of these drugs over years and small differences occurred likely by chance.

Table 5 – DDD of advanced therapies supplied in the **one year follow-up** and % day covered, overall and stratified by year of cohort entry

Drug	Total number of DDD	DDDs/365 days mean (±SD)	2015			2016			2017			2018			2019		
			Patients, n (%)	Total number of DDD, Number (%)	DDDs/365 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365 days mean, (± SD)
Adalimumab (N=239)	81986	94 (±43)	62 (26%)	20993 (26%)	93 (±48)	36 (15%)	11917 (15%)	91 (±47)	41 (17%)	14151 (17%)	95 (±46)	44 (18%)	15724 (19%)	98 (±41)	56 (23%)	19200 (23%)	94 (±35)
Infliximab (N=175)	97016	152 (±86)	33 (19%)	17200 (18%)	143 (±77)	29 (17%)	19370 (20%)	183 (±88)	29 (17%)	16382 (17%)	155 (±97)	41 (23%)	22498 (23%)	150 (±90)	43 (25%)	21567 (22%)	137 (±76)
Golimumab (N=110)	48041	120 (±60)	35 (32%)	12590 (26%)	98 (±43)	33 (30%)	15843 (33%)	131 (±62)	17 (15%)	7651 (16%)	123 (±63)	15 (14%)	7138 (15%)	130 (±89)	10 (9%)	4819 (10%)	132 (±36)
Vedolizumab (N=107)	40556	104 (±38.63)	-	-	-	14 (13%)	5222 (13%)	102 (±42)	37 (35%)	14722 (36%)	109 (±42)	27 (25%)	10389 (26%)	105 (±34)	29 (27%)	10222 (25%)	97 (±38)

Table 6– DDD of advanced therapies supplied in the **two years follow-up** and % day covered, overall and stratified by year of cohort entry

Drug	Total number of DDD	DDDs/365x2 days mean, (± SD)	2015			2016			2017			2018		
			Patients, n (%)	Total number of DDD, Number (%)	DDDs/365x2 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365x2 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365x2 days mean, (± SD)	Patients, n (%)	Total number of DDD, Number (%)	DDDs/365x2 days mean, (± SD)
Adalimumab (N=181)	93765	71 (±41)	62 (34%)	30896 (33%)	68(±41)	36 (20%)	18952 (20%)	72 (±42)	41 (23%)	20717 (22%)	69 (±44)	42 (23%)	23200 (25%)	76 (±40)
Infliximab (N=130)	108663	114 (±78)	33 (25%)	24100 (22%)	100(±68)	29 (22%)	28711 (26%)	136 (±86)	27 (21%)	21807 (20%)	111 (±79)	41 (32%)	34044 (31%)	114 (±81)
Golimumab (N=100)	59517	81 (±57)	35 (35%)	17741 (30%)	69(±45)	33 (33%)	21626 (36%)	90 (±61)	17 (17%)	11024 (19%)	89 (±67)	15 (15%)	9126 (15%)	83 (±63)
Vedolizumab (N=78)	47945	84 (±38)	-	-	-	14 (18%)	7723 (16%)	76 (±41)	37 (47%)	21834 (46%)	81 (±40)	27 (35%)	18389 (38%)	93 (±33)

Table 7 – Patients receiving advanced therapies other than the index drug in **the one year follow-up** period

Drug	Adalimumab	Infliximab	Golimumab	Vedolizumab
Overall, N	239	175	110	107
At least 1 index drug*, N (%)	26 (11%)	26 (15%)	24 (22%)	8 (8%)
Only 1 index drug, N (%)	26 (11%)	22 (13%)	24 (22%)	8 (8%)
Any combination of 2 index drugs, N (%)	-	4 (2%)	-	-
Any combination of 3 index drugs, N (%)	-	-		
All 4 index drugs, N (%)	-	-		
Tofacitinib, N (%)	-	-	-	-
Adalimumab, N (%)	x	8 (5%)	9 (8%)	-
Infliximab, N (%)	16 (7%)	x	11 (11%)	7 (7%)
Golimumab, N (%)	5 (2%)	5 (3%)	x	1 (1%)
Vedolizumab, N (%)	5 (2%)	17 (10%)	4 (4%)	x

* this number include patients with more than one index drug

Table 8 – Patients receiving advanced therapies other than the index drug in the **two years follow-up** period

Drug	Adalimumab	Infliximab	Golimumab	Vedolizumab
Overall, N	181	130	100	78
At least 1 index drug*, N (%)	40 (22%)	38 (29%)	40 (40%)	7 (9%)
Only 1 index drug, N (%)	37 (20%)	34 (26%)	35 (35%)	7 (9%)
Any combination of 2 index drugs, N (%)	3 (2%)	4 (3%)	5 (5%)	-
Any combination of 3 index drugs, N (%)	-	-		
All 4 index drugs, N (%)	-	-		
Tofacitinib, N (%)	-	-	-	-
Adalimumab, N (%)	x	14 (11%)	12 (12%)	2 (3%)
Infliximab, N (%)	29 (16%)	x	21 (21%)	5 (6%)
Golimumab, N (%)	7 (4%)	4 (3%)	x	-
Vedolizumab, N (%)	7 (4%)	24 (18%)	12 (12%)	x

* this number include patients with more than one index drug

Figure 5 –Time free from advanced therapy different and from any index drug (survival analysis) in the **one year follow-**up periods (Kaplan-Mayer)

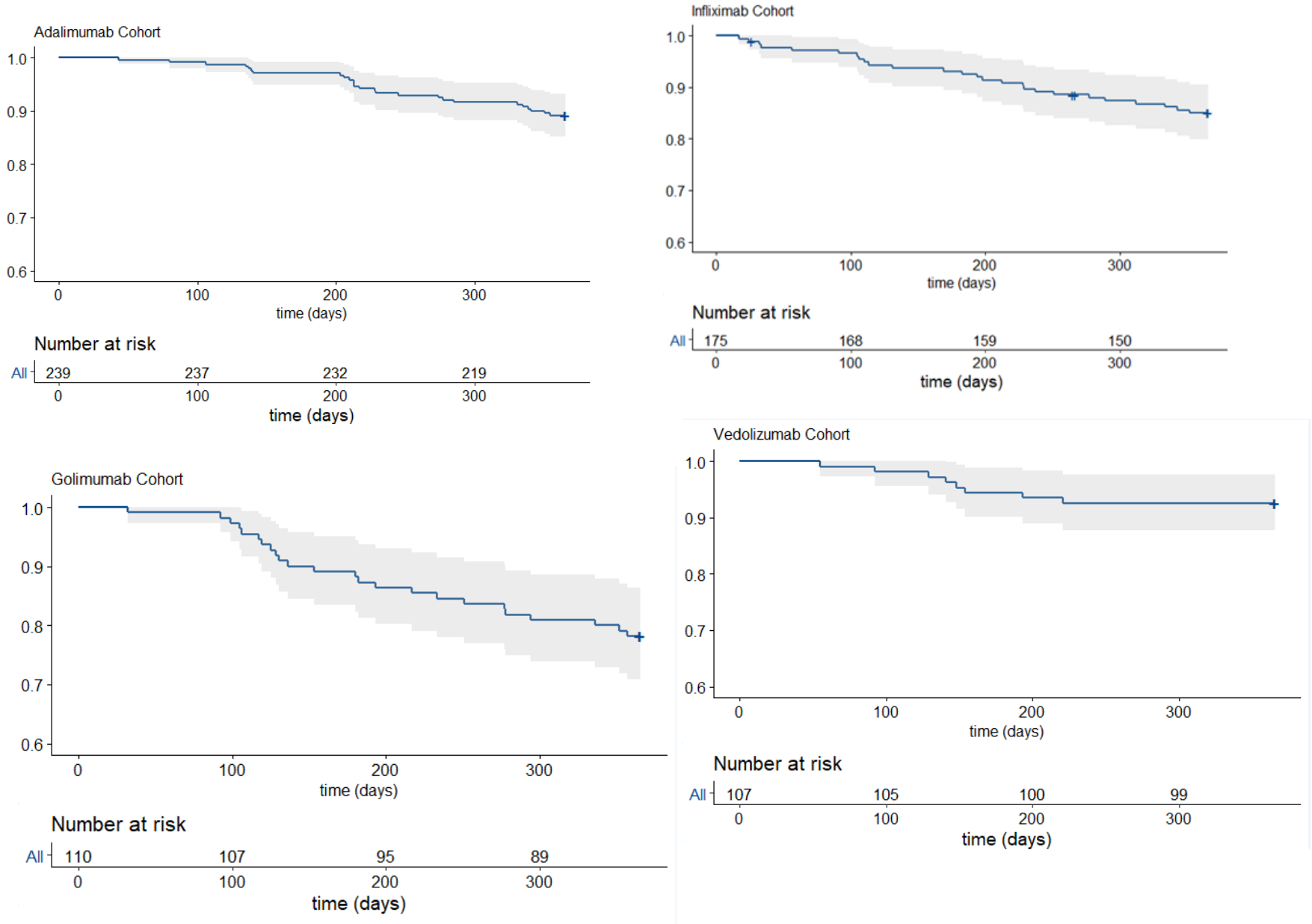


Figure 6 –Time free from advanced therapy different and from any index drug (survival analysis) in the **two years follow-up** periods (Kaplan-Mayer)

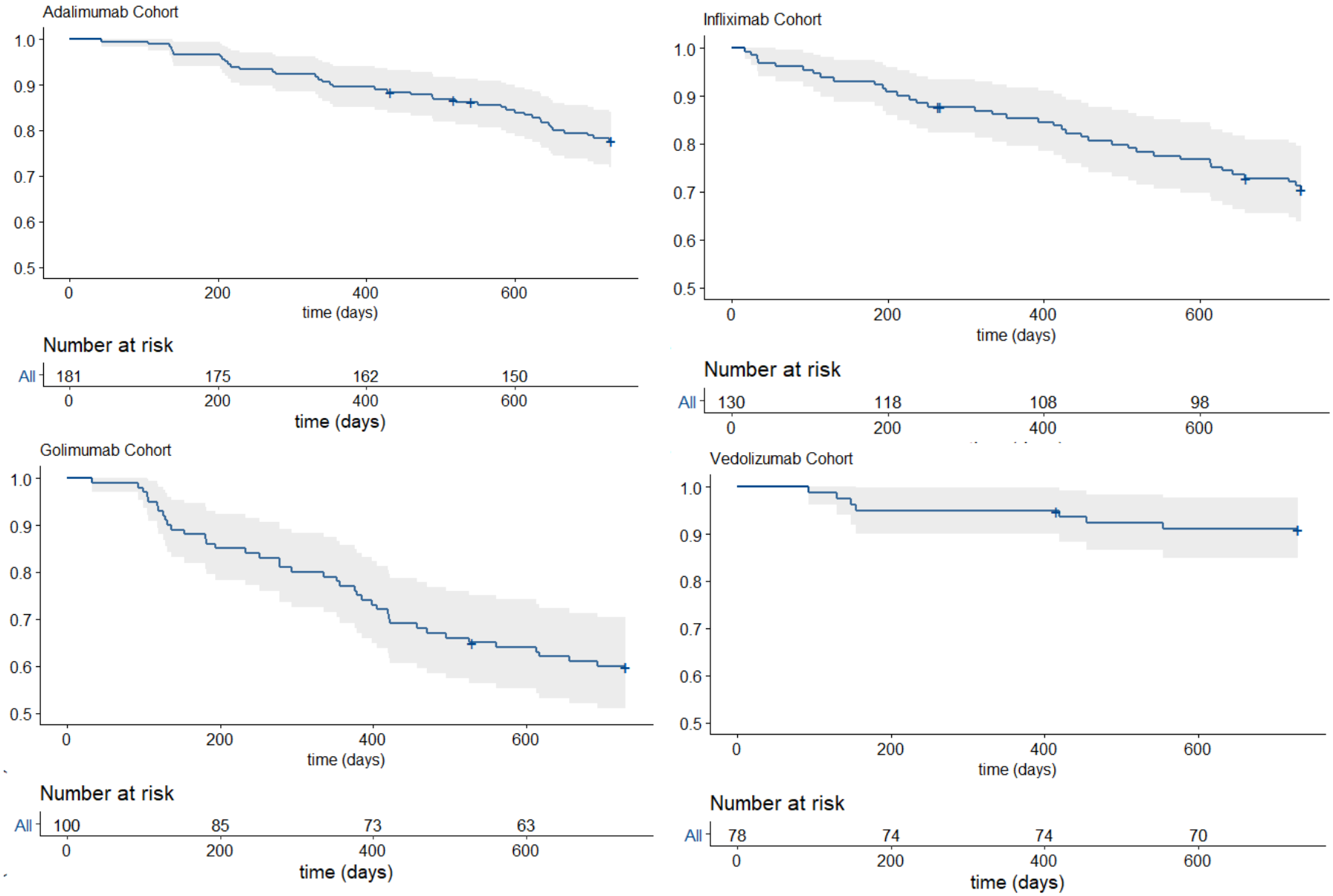


Table 9 – Patients receiving at least one supply of each drug of interest drug in the **one year follow-up** period

Drug	Adalimumab	Infliximab	Golimumab	Vedolizumab
Overall, N	239	175	110	107
Other biologics, N (%)	5 (2%)	1 (1%)	-	-
Antibiotics, N (%)	157 (66%)	119 (68%)	80 (73%)	71 (66%)
Salicilates, N (%)	18 (8%)	7 (4%)	11 (10%)	10 (9%)
Mesalazine , N (%)	138 (58%)	121(69%)	87 (79%)	81 (76%)
Azathioprine , N (%)	22 (9%)	19 (11%)	12 (11%)	8 (7%)
Methotrexate , N (%)	15 (6%)	1 (1%)	13 (12%)	4 (4%)
Ciclosporin , N (%)	-	1 (1%)	-	1 (1%)
6-MP , N (%)	2 (1%)	1 (1%)	-	2 (2%)
Corticosteroids (systemic) , N (%)	105 (44%)	128 (73%)	64 (58%)	64 (60%)
Corticosteroids (local) , N (%)	63 (26%)	69 (39%)	59 (54%)	51 (48%)
Tacrolimus , N (%)n (%)	-	-	-	-

Table 10 – Patients receiving at least one supply of each drug of interest in the **two years follow-up** period

Drug	Adalimumab	Infliximab	Golimumab	Vedolizumab
Overall, N	181	130	100	78
Other biologics , N (%)	8 (4%)	1 (1%)	1 (1%)	-
Antibiotics, N (%)	141 (78%)	110 (85%)	84 (84%)	68 (87%)
Salicilates , N (%)	18 (10%)	8 (6%)	10 (10%)	10 (13%)
Mesalazine , N (%)	112 (62%)	103 (79%)	82 (82%)	63 (81%)
Azathioprine , N (%)	24 (13%)	23 (18%)	12 (12%)	8 (10%)
Methotrexate , N (%)	11 (6%)	3 (2%)	13 (13%)	5 (6%)
Ciclosporin , N (%)	1 (1%)	2 (2%)	-	1 (1%)
6-MP , N (%)	4 (2%)	2 (2%)	-	-
Corticosteroids (systemic) , N (%)	103 (57%)	110 (85%)	68 (68%)	58 (74%)
Corticosteroids (local) , N (%)	64 (35%)	66 (51%)	65 (65%)	50 (64%)
Tacrolimus , N (%)	-	-	-	-

Table 11 – DDD of advanced therapies other than the index drug supplied in the **one year follow-up**, overall and stratified by year of cohort entry

Drug	Patients*	Number of DDD**	2015		2016		2017		2018		2019	
			Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)
Adalimumab (N=239)												
Tofacitininb	-	-	-	-	-	-	-	-	-	-	-	-
Infliximab	16	5813	7 (44%)	2747 (47%)	-	-	1 (6%)	320 (6%)	3 (19%)	667 (11%)	5 (31%)	2080(36%)
Golimumab	5	1145	3 (60%)	813 (71%)	1 (20%)	301 (26%)	1 (20%)	30 (3%)	-	-	-	-
Vedolizumab	5	1167	-	-	-	-	3 (60%)	722 (62%)	-	-	2 (40%)	445 (38%)
Infliximab (N=175)												
Tofacitininb	-	-	-	-	-	-	-	-	-	-	-	-
Adalimumab	8	2110	4 (50%)	938 (44%)	-	-	1 (13%)	552 (26%)	-	-	3 (38%)	621 (29%)
Golimumab	5	1355	2 (40%)	723 (53%)	1 (20%)	422 (31%)	1 (20%)	90 (7%)	-	-	1 (20%)	120 (9%)
Vedolizumab	17	3167	1 (6%)	222 (7%)	3 (18%)	667 (21%)	5 (29%)	944 (30%)	4 (24%)	667 (21%)	4 (24%)	667 (21%)
Golimumab (N=110)												
Tofacitininb	-	-	-	-	-	-	-	-	-	-	-	-
Adalimumab	9	1448	3 (33%)	386 (27%)	2 (22%)	345 (24%)	2 (22%)	469 (32%)	1 (11%)	110 (8%)	1 (11%)	138 (10%)
Infliximab	11	5145	3 (27%)	1440 (28%)	4 (36%)	2320 (45%)	3 (27%)	1172 (23%)	1 (9%)	213 (4%)	-	-
Vedolizumab	4	889	1 (25%)	278 (31%)	2 (50%)	167 (19%)	1 (25%)	444 (50%)	-	-	-	-
Vedolizumab (N=107)												
Tofacitininb	-	-	-	-	-	-	-	-	-	-	-	-
Adalimumab	-	-	-	-	-	-	-	-	-	-	-	-
Infliximab	7	1253	-	-	1 (14%)	107 (8%)	2 (29%)	347 (28%)	1 (14%)	267 (21%)	3 (43%)	533 (43%)
Golimumab	1	120	-	-	-	-	-	-	-	-	1 (100%)	120(100%)

*each patient could have received more than 1 advanced therapy, therefore the sum could not coincide with the number of patients with at least 1 advanced therapy; **Overall number of DDD administered over 1 year (100%)

Table 12 – DDD of advanced therapies other than the index drug supplied in the **two years follow-up**, overall and stratified by year of cohort entry

Drug	Patients*	Number of DDD**	2015		2016		2017		2018	
			Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)
Adalimumab (N=181)										
Tofacitininb	-	-	-	-	-	-	-	-	-	-
Infliximab	29	13343	16 (55%)	7840 (59%)	1 (3%)	80 (1%)	7 (24%)	1893 (14%)	5 (17%)	3529 (26%)
Golimumab	7	3102	3 (43%)	1717 (55%)	1 (14%)	1024 (33%)	2 (29%)	120 (4%)	1 (14%)	241 (8%)
Vedolizumab	7	2667	3 (43%)	611 (23%)	1 (14%)	167 (6%)	3 (43%)	1889 (71%)	-	-
Infliximab (N=130)										
Tofacitininb	-	-	-	-	-	-	-	-	-	-
Adalimumab	14	4441	7 (50%)	2676 (60%)	3 (21%)	386 (9%)	2 (14%)	772 (17%)	2 (14%)	607 (14%)
Golimumab	4	1476	2 (50%)	723 (49%)	1 (25%)	663 (45%)	1 (25%)	90 (6%)	-	-
Vedolizumab	24	9278	3 (13%)	1222 (13%)	8 (33%)	3167 (34%)	7 (29%)	2611 (28%)	6 (25%)	2278 (25%)
Golimumab (N=100)										
Tofacitininb	-	-	-	-	-	-	-	-	-	-
Adalimumab	12	3793	4 (33%)	883 (23%)	2 (17%)	1034 (27%)	3 (25%)	1186 (31%)	3 (25%)	690 (18%)
Infliximab	21	16239	4 (19%)	3147 (19%)	7 (33%)	5760 (35%)	5 (24%)	3945 (24%)	5 (24%)	3387 (21%)
Vedolizumab	12	3389	3 (25%)	889 (26%)	5 (42%)	1444 (43%)	3 (25%)	889 (26%)	1 (8%)	167 (5%)
Vedolizumab (N=78)										
Tofacitininb	-	-	-	-	-	-	-	-	-	-
Adalimumab	2	276	-	-	-	-	2 (100%)	276 (100%)	-	-
Infliximab	5	1493	-	-	1 (20%)	107 (7%)	3 (60%)	1120 (75%)	1 (20%)	267 (18%)
Golimumab	-	-	-	-	-	-	-	-	-	-

*each patient could have received more than 1 advanced therapy, therefore the sum could not coincide with the number of patients with at least 1 advanced therapy;

**Overall number of DDD administered over 2 years (100%)

Table 13 – DDD of other drugs of interest supplied in the **one year follow-up**, overall and stratified by year of cohort entry

Drug	Patients	Number of DDD	2015		2016		2017		2018		2019	
			Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)
Adalimumab(N=239)												
Other biologics	5	784	-	-	1 (20%)	229 (29%)	1 (20%)	300 (38%)	3 (60%)	256 (33%)	-	-
Antibiotics	157	2980	45 (29%)	949 (32%)	23 (15%)	300 (10%)	26 (17%)	545 (18%)	31 (20%)	755 (25%)	32 (20%)	430 (14%)
Salicilates	18	2874	5 (28%)	574 (20%)	4 (22%)	875 (30%)	4 (22%)	725 (25%)	1 (6%)	75 (3%)	4 (22%)	625 (22%)
Mesalazine	138	79021	34 (25%)	16459 (21%)	19 (14%)	9387 (12%)	24 (17%)	14404 (18%)	28 (20%)	17364 (22%)	33 (24%)	21407 (27%)
Azathioprine	22	3350	11 (50%)	1500 (45%)	3 (14%)	583 (17%)	3 (14%)	583 (17%)	2 (9%)	267 (8%)	3 (14%)	417 (12%)
Methotrexate	15	2105	4 (27%)	552 (26%)	1 (7%)	208 (10%)	2 (13%)	416 (20%)	1 (7%)	24 (1%)	7 (47%)	905 (43%)
Cyclosporin	-	-	-	-	-	-	-	-	-	-	-	-
6-MP	2	158	1 (50%)	108 (68%)	-	-	1 (50%)	50 (32%)	-	-	-	-
Corticosteroids (systemic)	105	16693	27 (26%)	5434 (33%)	18 (17%)	3032 (18%)	17 (16%)	2682 (16%)	18 (17%)	2661 (16%)	25 (24%)	2884 (17%)
Crticosteroids (local)	63	6328	25 (40%)	2666 (42%)	10 (16%)	677 (11%)	7 (11%)	820 (13%)	9 (14%)	1470 (23%)	12 (19%)	695 (11%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-	-	-
Infliximab (N=175)												
Other biologics	1	371	-	-	-	-	-	-	1 (100%)	371 (100%)	-	-
Antibiotics	119	5414	25 (21%)	419 (8%)	20 (17%)	626 (12%)	19 (16%)	829 (15%)	29 (24%)	2431 (45%)	26 (22%)	1109 (20%)
Salicilates	7	1048	-	-	4 (57%)	948 (90%)	1 (14%)	12 (1%)	1 (14%)	37 (4%)	1 (14%)	50 (5%)
Mesalazine	121	73550	24 (20%)	13928 (19%)	23 (19%)	11512 (16%)	23 (19%)	17185 (23%)	27 (22%)	17466 (24%)	24 (20%)	13460 (18%)
Azathioprine	19	2567	9 (47%)	1183 (46%)	5 (26%)	867 (34%)	1 (5%)	50 (2%)	2 (11%)	100 (4%)	2 (11%)	367 (14%)
Methotrexate	1	13	-	-	-	-	1 (100%)	13 (100%)	-	-	-	-
Cyclosporin	1	180	-	-	1 (100%)	180 (100%)	-	-	-	-	-	-
6-MP	1	17	1 (100%)	17 (100%)	-	-	-	-	-	-	-	-
Corticosteroids (systemic)	128	18670	26 (20%)	4518 (24%)	24 (19%)	3590 (19%)	20 (16%)	3040 (16%)	31 (24%)	3361 (18%)	27 (21%)	4162 (22%)
Crticosteroids (local)	69	6227	20 (29%)	2318 (37%)	14 (20%)	1464 (24%)	10 (14%)	781 (13%)	13 (19%)	814 (13%)	12 (17%)	850 (14%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-	-	-
Golimumab (N=110)												
Other biologics	-	-	-	-	-	-	-	-	-	-	-	-
Antibiotics	80	1925	27 (34%)	758 (39%)	26 (33%)	695 (36%)	12 (15%)	253 (13%)	9 (11%)	122 (6%)	6 (8%)	96 (5%)
Salicilates	11	2824	5 (45%)	1400 (50%)	4 (36%)	924 (33%)	1 (9%)	300 (11%)	-	-	1 (9%)	200 (7%)
Mesalazine	87	56864	28 (32%)	17348 (31%)	29 (33%)	17722 (31%)	13 (15%)	9731 (17%)	11 (13%)	8054 (14%)	6 (7%)	4009 (7%)
Azathioprine	12	2133	1 (8%)	200 (9%)	2 (17%)	433 (20%)	4 (33%)	983 (46%)	3 (25%)	200 (9%)	2 (17%)	317 (15%)
Methotrexate	13	1937	7 (54%)	944 (49%)	2 (15%)	480 (25%)	2 (15%)	233 (12%)	2 (15%)	280 (14%)	-	-
Cyclosporin	-	-	-	-	-	-	-	-	-	-	-	-
6-MP	-	-	-	-	-	-	-	-	-	-	-	-

Drug	Patients	Number of DDD	2015		2016		2017		2018		2019	
			Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)
Corticosteroids (systemic)	64	12723	25 (39%)	4730 (37%)	21 (33%)	4627 (36%)	8 (13%)	1774 (14%)	6 (9%)	944 (7%)	4 (6%)	649 (5%)
Crticosteroids (local)	59	7457	17 (29%)	2613 (35%)	21 (36%)	2180 (29%)	11 (19%)	1204 (16%)	8 (14%)	1210 (16%)	2 (3%)	250 (3%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-	-	-
Vedolizumab (N=107)												
Other biologics	-	-	-	-	-	-	-	-	-	-	-	-
Antibiotics	71	2003	-	-	8 (11%)	372 (19%)	27 (38%)	896 (45%)	18 (25%)	363 (18%)	18 (25%)	371 (19%)
Salicilates	10	2412	-	-	2 (20%)	387 (16%)	2 (20%)	75 (3%)	5 (50%)	1375 (57%)	1 (10%)	575 (24%)
Mesalazine	81	60842	-	-	11 (14%)	8103 (13%)	29 (36%)	22507 (37%)	18 (22%)	15577 (26%)	23 (28%)	14655(24%)
Azathioprine	8	1083	-	-	-	-	6 (75%)	800 (74%)	2 (25%)	283 (26%)	-	-
Methotrexate	4	400	-	-	1 (25%)	88 (22%)	1 (25%)	48 (12%)	2 (50%)	264 (66%)	-	-
Cyclosporin	1	288	-	-	-	-	1 (100%)	288 (100%)	-	-	-	-
6-MP	2	158	-	-	-	-	-	-	-	-	2 (100%)	158 (100%)
Corticosteroids (systemic)	64	10508	-	-	9 (14%)	1113 (11%)	22 (34%)	5546 (53%)	16 (25%)	1665 (16%)	17 (27%)	2184 (21%)
Crticosteroids (local)	51	5507	-	-	6 (12%)	860 (16%)	20 (39%)	2291 (42%)	17 (33%)	1689 (31%)	8 (16%)	667 (12%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-	-	-

Table 14 – DDD of other drugs of interest (table 2) supplied in the **two years follow-up**, overall and stratified by year of cohort entry

Drug	Patients	Number of DDD	2015		2016		2017		2018	
			Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)
Adalimumab (N=175)										
Other biologics	8	1681	1 (13%)	30 (2%)	1 (13%)	514 (31%)	2 (25%)	676 (40%)	4 (50%)	462 (27%)
Antibiotics	141	4761	50 (35%)	1999 (42%)	28 (20%)	701 (15%)	30 (21%)	941 (20%)	33 (23%)	1120 (24%)
Salicilates	18	5011	5 (28%)	1198 (24%)	6 (33%)	1787 (36%)	5 (28%)	1650 (33%)	2 (11%)	375 (7%)
Mesalazine	112	106132	37 (33%)	30779 (29%)	22 (20%)	16971 (16%)	25 (22%)	28716 (27%)	28 (25%)	29666 (28%)
Azathioprine	24	6017	15 (63%)	3617 (60%)	4 (17%)	1117(19%)	3 (13%)	1000 (17%)	2 (8%)	283 (5%)
Methotrexate	11	1829	5 (45%)	954 (52%)	1 (9%)	208 (11%)	3 (27%)	507 (28%)	2 (18%)	160 (9%)
Cyclosporin	1	20	-	-	-	-	-	-	1 (100%)	20 (100%)
6-MP	4	308	3 (75%)	233 (76%)	-	-	1 (25%)	75 (24%)	-	-
Corticosteroids (systemic)	103	22508	36 (35%)	9276 (41%)	21 (20%)	5188 (23%)	24 (23%)	4316 (19%)	22 (21%)	3728 (17%)
Crticosteroids (local)	64	10315	29 (45%)	4433 (43%)	12 (19%)	1293 (13%)	12 (19%)	1683 (16%)	11 (17%)	2906 (28%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-
Infliximab (N=130)										
Other biologics	1	714	-	-	-	-	-	-	1 (100%)	714 (100%)
Antibiotics	110	7339	28 (25%)	802 (11%)	27 (25%)	1121 (15%)	21 (19%)	1113 (15%)	34 (31%)	4303 (59%)
Salicilates	8	1846	-	-	5 (63%)	1746 (95%)	1 (13%)	12 (1%)	2 (25%)	87 (5%)
Mesalazine	103	112826	25 (24%)	25090 (22%)	25 (24%)	21406 (19%)	22 (21%)	30995 (27%)	31 (30%)	35335 (31%)
Azathioprine	23	5050	12 (52%)	2967 (59%)	5 (22%)	1650 (33%)	3 (13%)	200 (4%)	3 (13%)	233 (5%)
Methotrexate	3	125	-	-	1 (33%)	36 (29%)	1 (33%)	29 (23%)	1 (33%)	60 (48%)
Cyclosporin	2	286	-	-	1 (50%)	180 (63%)	-	-	1 (50%)	106 (37%)
6-MP	2	50	2 (100%)	50 (100%)	-	-	-	-	-	-
Corticosteroids (systemic)	110	23880	27 (25%)	6552(27%)	27 (25%)	6173 (26%)	21 (19%)	5080 (21%)	35 (32%)	6075 (25%)
Crticosteroids (local)	66	8757	20 (30%)	3331 (38%)	16 (24%)	2848 (33%)	15 (23%)	1151(13%)	15 (23%)	1427 (16%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-
Golimumab (N=100)										
Other biologics	1	286	1 (100%)	286 (100%)	-	-	-	-	-	-
Antibiotics	84	3355	32 (38%)	1504 (45%)	29 (35%)	1200 (36%)	12 (14%)	386 (12%)	11 (13%)	264 (8%)
Salicilates	10	5173	5 (50%)	2925 (57%)	4 (40%)	1698 (33%)	1 (10%)	550 (11%)	-	-
Mesalazine	82	96752	28 (34%)	28613 (30%)	30 (37%)	35524 (37%)	13 (16%)	17840 (18%)	11 (13%)	14774 (15%)
Azathioprine	12	3400	2 (17%)	483 (14%)	3 (25%)	1050 (31%)	4 (33%)	1667 (49%)	3 (25%)	200 (6%)
Methotrexate	13	3846	7 (54%)	2045 (53%)	2 (15%)	704 (18%)	2 (15%)	673 (17%)	2 (15%)	424 (11%)
Cyclosporin	-	-	-	-	-	-	-	-	-	-
6-MP	-	-	-	-	-	-	-	-	-	-

Drug	Patients	Number of DDD	2015		2016		2017		2018	
			Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)	Patients (%)	Number of DDD (%)
Corticosteroids (systemic)	68	22055	28 (41%)	9083 (41%)	22 (32%)	7702 (35%)	10 (15%)	3613 (16%)	8 (12%)	1657 (8%)
Crticosteroids (local)	65	12809	21 (32%)	4811 (38%)	22 (34%)	4308 (34%)	12 (18%)	1904 (15%)	10 (15%)	1786 (14%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-
Vedolizumab (N=78)										
Other biologics	-	-	-	-	-	-	-	-	-	-
Antibiotics	68	3039	-	-	12 (18%)	562 (18%)	34 (50%)	1672 (55%)	22 (32%)	804 (26%)
Salicilates	10	3537	-	-	2 (20%)	612 (17%)	3 (30%)	125 (4%)	5 (50%)	2800 (79%)
Mesalazine	63	82942	-	-	11 (17%)	11924 (14%)	31 (49%)	42747 (52%)	21 (33%)	28271 (34%)
Azathioprine	8	1367	-	-	-	-	6 (75%)	917 (67%)	2 (25%)	450 (33%)
Methotrexate	5	1304	-	-	2 (40%)	256 (20%)	1 (20%)	208 (16%)	2 (40%)	840 (64%)
Cyclosporin	1	552	-	-	-	-	1 (100%)	552 (100%)	-	-
6-MP	0	0	-	-	-	-	-	-	-	-
Corticosteroids (systemic)	58	13263	-	-	11 (19%)	1477 (11%)	29 (50%)	9014 (68%)	18 (31%)	2772 (21%)
Crticosteroids (local)	50	7442	-	-	7 (14%)	1260 (17%)	23 (46%)	3319 (45%)	20 (40%)	2863 (38%)
Tacrolimus	-	-	-	-	-	-	-	-	-	-

6.3 Research question 3

Table 15 shows ED accesses, hospitalizations, and gastroenterological visits in the first year and in the second year of follow up for each index drug. The percentages of users who accessed to ED at least once in the first year were similar in the four cohorts and ranged between 36% (adalimumab) and 40% (vedolizumab). Time free from ED accesses was longer for adalimumab (176 days) than for the other index drugs. Males showed to have at least one ED access more frequently than females except for vedolizumab, where the numbers between the two were similar. The number of patients with at least one hospitalization ranged between 26% (adalimumab) and 35% (infliximab). In this case, a high percentage of males was observed for golimumab and infliximab while it is quite similar for adalimumab and vedolizumab. When the mean time to first hospitalization was analyzed for vedolizumab occurred 166 days. The percentage of users with at least one gastroenterological visit was highly variable and varied between 12% (patients with infliximab as an index drug) and 54% (subjects with golimumab as an index drug). This trend may be consistent with the continuation of therapy observed for golimumab, which has the highest switching rate in the first and second years of treatment. It is possible that patients switching to other advanced therapies required gastroenterological visits more often. Trends in ED accesses, hospitalization, and gastroenterological visits were also confirmed in the second year of follow-up where the number of males with at least one access was always high in all categories and medications of interest.

The most frequent causes of ED access observed in the year preceding the index date (**table 18**) included disease of the gastrointestinal system (17-22%) probably due to the underlying pathology, signs and symptoms of defined diseases (23-29%) and injuries and poisonings (9-25%). Furthermore, in the vedolizumab cohort, 14% of ED were caused by pathologies of the nervous system and sense organs, while in the other patient groups, these percentages are halved. This result is difficult to interpret.

In the first year of follow-up (table 19), ED accesses are attributed, with percentages similar to the year preceding the index date, to the gastrointestinal system (9-14%), signs and symptoms of defined diseases (22-35%) and injuries and poisonings (15-25%). In this case, pathologies of the nervous system and sense organs are quite frequent not only for vedolizumab (as observed in the previous year) but also for the other index drugs (9-15%). These data are confirmed at two years of follow-up (table 20).

The hospitalizations in the year preceding the index date were mainly caused by infectious diseases (58-66%), followed by those for gastrointestinal causes (14-22%). This trend is maintained in the first (table 22) and second year of follow-up (table 23). The modest reduction of hospitalizations, particularly in the first year of follow-up, compared with the year preceding the index date could be explained by a general improvement of the patients, associated with the introduction of the new advanced therapy.

Of note, these drugs are associated with the development of infections due to their immuno-modulating action. However, these hospitalizations do not necessarily mean a causal association with the drugs supplied to the patients. As a general remind, in the Tuscan administrative database patients are recorded with a unique cause of access in Emergency department. This cause is usually the main symptom and rarely report a complete diagnosis. Hospital discharge records contain 6 causes of hospitalization (1 primary and 5 secondary) and frequently reported specific diagnosis. Therefore, there is not a correspondence between ED access and Hospital discharge records. For instance, a patient could be admitted to ED with “fever” and then, after a full examination, hospitalized with a diagnosis of infection. For this reason, infections are more frequently reported as causes of hospitalization than as causes of Ed access.

Table 15 - Number of Emergency department (ED) admissions, hospitalizations, specialist visits (gastroeneterological) in the first and second year of follow-up

Drug	New users, N		ED admissions, N		Hospitalizations, N		Gastroenterological visits, N	
	1-year	2-years	1-year	2-years	1-year	2-years	1 year	2-year
Adalimumab	239	181	139	194	83	155	335	611
Infliximab	175	130	112	163	111	169	172	372
Golimumab	110	100	71	127	60	114	268	509
Vedolizumab	107	78	77	99	60	87	97	127

Table 16 - Number of patients with at least 1 Emergency department (ED) admission, hospitalization, and specialist visit (gastroenterological) in **the one-year follow-up**, and mean time to first event overall and stratified by gender

	ED admissions				Hospitalizations				Gastroenterological visits			
	Patients N (%)	Mean time (days) to first event (±SD) / Median (±IQ)	M N (%)	F N (%)	Patients N (%)	Mean time (days) to first event (±SD) / Median (±IQ)	M N (%)	F N (%)	Patients N (%)	Mean time (days) to first event (±SD) / Median (±IQ)	M N (%)	F N(%)
Adalimumab (N = 239)	85 (36%)	176 (±107.71) / 184 (±164)	47 (55%)	38 (45%)	54 (26%)	158 (±103.45) / 162 (±177.75)	26 (48%)	28 (52%)	96 (40%)	111 (±95.62) / 81.5 (±154.75)	58 (60%)	38 (40%)
Infliximab (N = 175)	65 (37%)	140 (±104.04) / 117 (±183)	36 (55%)	29 (45%)	61 (35%)	141 (±106.35) / 134 (±168)	33 (54%)	28 (46%)	21 (12%)	99 (±94.74) / 85 (±116)	9 (43%)	12 (57%)
Golimumab (N = 110)	42 (38%)	157 (±92.22) / 162 (±125.5)	25 (60%)	17 (40%)	33 (30%)	139 (±111.39) / 119 (±220)	21 (64%)	12 (36%)	59 (54%)	94 (±85.44) / 63 (±100)	33 (56%)	26 (44%)
Vedolizumab (N =107)	43 (40%)	161 (±117.52) / 127 (±225)	21 (49%)	22 (51%)	31 (29%)	166 (±106.25) / 161 (±189)	16 (52%)	15 (48%)	13 (30%)	114 (±116.93) / 96 (±182)	8 (62%)	5 (38%)

Table 17 - Number of patients with at least 1 Emergency department (ED) admission, hospitalization, and specialist visit (gastroenterological) in **the two-year follow-up**, and mean time to first event overall and stratified by gender

	ED admissions				Hospitalizations				Gastroenterological visits			
	Patients N (%)	Mean time (days) to first event (±SD) / Median (±IQ)	M N (%)	F N (%)	Patients N (%)	Mean time (days) to first event (±SD) / Median (±IQ)	M N (%)	F N (%)	Patients N (%)	Mean time (days) to first event (±SD) / Median (±IQ)	M N (%)	F N(%)
Adalimumab (N = 181)	100 (55%)	297 (±200.02) / 260.5 (±300)	56 (56%)	44 (44%)	73 (40%)	305 (±209.42) / 273 (±344)	39 (53%)	34 (47%)	95 (52%)	189 (±186.28) / 108 (±208)	53 (52%)	42 (48%)
Infliximab (N = 130)	71 (55%)	266 (±207.44) / 255 (±355.5)	42 (59%)	29 (41%)	67 (52%)	235 (±191.42) / 169 (±256.5)	37 (55%)	30 (45%)	22 (17%)	148 (±151.51) / 85 (±187)	10 (45%)	12 (55%)
Golimumab (N =100)	52 (52%)	247 (±187.42) / 190 (±230.5)	33 (63%)	19 (27%)	46 (46%)	263 (±215.92) / 239.5 (±311.5)	25 (54%)	21 (46%)	58 (58%)	118 (±125.89) / 67 (±126)	35 (60%)	23 (40%)
Vedolizumab (N =78)	46 (59%)	273 (±191.8) / 286 (±316)	26 (57%)	20 (43%)	36 (46%)	283 (±183.74) / 275 (±257.5)	22 (61%)	14 (39%)	10 (13%)	135.6 (±153) / 111.5 (±167.5)	7 (70%)	3 (30%)

Table 18 - Number and Causes of Emergency department admission in the **year before cohort entry**

		Adalimumab (N=151)	Infliximab (N=181)	Golimumab (N=55)	Vedolizumab (N=105)
Description	ICD-9 code	N (%)	N (%)	N (%)	N (%)
Infectious and parasitic diseases	001-139	9 (6.0%)	11 (6.1%)	1 (1.8%)	3 (2.9%)
Neoplasms	139-239	-	-	1 (1.8%)	1 (1.0%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	3 (2.0%)	2 (1.1%)	-	-
Diseases of the blood and blood-forming organs	280-289	1 (0.7%)	9 (5.0%)	-	1 (1.0%)
Mental disorders	290-319	2 (1.3%)	3 (1.7%)	-	3 (2.9%)
Diseases of the nervous system and sense organs	320-389	6 (4.0%)	12 (6.6%)	4 (7.3%)	15 (14.3%)
Diseases of the circulatory system	390-459	5 (3.3%)	2 (1.1%)	3 (5.5%)	3 (2.9%)
Diseases of the respiratory system	460-519	2 (1.3%)	3 (1.7%)	1 (1.8%)	2 (1.9%)
Diseases of the digestive system	520-579	34 (22.5%)	59 (32.6%)	11 (20.0%)	18 (17.1%)
Diseases of the genitourinary system	580-629	2 (1.3%)	4 (2.2%)	1 (1.8%)	1 (1.0%)
Complications of pregnancy, childbirth, and the puerperium	630-679	-	-	-	-
Diseases of the skin and subcutaneous tissue	680-709	4 (2.6%)	3 (1.7%)	1 (1.8%)	1 (1.0%)
Diseases of the musculoskeletal system and connective tissue	710-739	7 (4.6%)	3 (1.7%)	2 (3.6%)	6 (5.7%)
Congenital Anomalies	740-759	-	-	-	-
Certain Conditions Originating In The Perinatal Period	760-779	-	-	-	-
Symptoms, signs, and ill-defined conditions	780-799	44 (29.1%)	44 (24.3%)	13 (23.6%)	27 (25.7%)
Injury and poisoning	800-999	27 (17.9%)	16 (8.8%)	14 (25.5%)	18 (17.1%)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	5 (3.3%)	10 (5.5%)	3 (5.5%)	6 (5.7%)

Table 19 - Number and causes of Emergency department admission in the **one-year follow-up**

		Adalimumab (N=139)	Infliximab (N=112)	Golimumab (N=71)	Vedolizumab (N=77)
Description	ICD-9 code	N (%)	N (%)	N (%)	N (%)
Infectious and parasitic diseases	001-139	5 (3.6%)	7 (6.3%)	-	5 (6.5%)
Neoplasms	139-239	-	-	-	-
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	-	2 (1.8%)	-	-
Diseases of the blood and blood-forming organs	280-289	3 (2.2%)	1 (0.9%)	2 (2.8%)	3 (3.9%)
Mental disorders	290-319	5 (3.6%)	2 (1.8%)	2 (2.8%)	1 (1.3%)
Diseases of the nervous system and sense organs	320-389	13 (9.4%)	17 (15.2%)	7 (9.9%)	9 (11.7%)
Diseases of the circulatory system	390-459	5 (3.6%)	7 (6.3%)	3 (4.2%)	1 (1.3%)
Diseases of the respiratory system	460-519	5 (3.6%)	5 (4.5%)	3 (4.2%)	3 (3.9%)
Diseases of the digestive system	520-579	12 (8.6%)	15 (13.4%)	10 (14.1%)	11 (14.3%)
Diseases of the genitourinary system	580-629	6 (4.3%)	-	2 (2.8%)	-
Complications of pregnancy, childbirth, and the puerperium	630-679	-	-	-	-
Diseases of the skin and subcutaneous tissue	680-709	5 (3.6%)	1 (0.9%)	-	1 (1.3%)
Diseases of the musculoskeletal system and connective tissue	710-739	8 (5.8%)	3 (2.7%)	4 (5.6%)	3 (3.9%)
Congenital Anomalies	740-759	-	-	-	-
Certain Conditions Originating In The Perinatal Period	760-779	-	-	-	-
Symptoms, signs, and ill-defined conditions	780-799	31 (22.3%)	27 (24.1%)	25 (35.2%)	17 (22.1%)
Injury and poisoning	800-999	31 (22.3%)	20 (17.9%)	11 (15.5%)	19 (24.7%)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	10 (7.2%)	5 (4.5%)	2 (2.8%)	4 (5.2%)

Output Table 20 - Number and Causes of Emergency department admission in the **two-year follow-up**

		Adalimumab (N=248)	Infliximab (N=203)	Golimumab (N=132)	Vedolizumab (N=123)
Description	ICD-9 code	N (%)	N (%)	N (%)	N (%)
Infectious and parasitic diseases	001-139	8 (3.2%)	11 (5.4%)	1 (0.8%)	8 (6.5%)
Neoplasms	139-239	-	-	1 (0.8%)	-
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	1 (0.4%)	3 (1.5%)	1 (0.8%)	-
Diseases of the blood and blood-forming organs	280-289	6 (2.4%)	2 (1.0%)	3 (2.3%)	6 (4.9%)
Mental disorders	290-319	8 (3.2%)	2(1.0%)	4 (3.0%)	1 (0.8%)
Diseases of the nervous system and sense organs	320-389	20 (8.1%)	26 (12.8%)	13 (9.8%)	14 (11.4%)
Diseases of the circulatory system	390-459	11 (4.4%)	10 (4.9%)	7 (5.3%)	3 (2.4%)
Diseases of the respiratory system	460-519	10 (4.0%)	7 (3.4%)	4 (3.0%)	3 (2.4%)
Diseases of the digestive system	520-579	29 (11.7%)	32 (15.8%)	17 (12.9%)	21 (17.1%)
Diseases of the genitourinary system	580-629	7 (2.8%)	1 (0.5%)	3 (2.3%)	1 (0.8%)
Complications of pregnancy, childbirth, and the puerperium	630-679	1 (0.4%)	-	-	-
Diseases of the skin and subcutaneous tissue	680-709	10 (4.0%)	4 (2.0%)	2 (1.5%)	2 (1.6%)
Diseases of the musculoskeletal system and connective tissue	710-739	12 (4.8%)	5 (2.5%)	8 (6.1%)	3 (2.4%)
Congenital Anomalies	740-759	-	-	-	-
Certain Conditions Originating In The Perinatal Period	760-779	-	-	-	-
Symptoms, signs, and ill-defined conditions	780-799	56 (22.6%)	48 (23.6%)	39 (29.5%)	27 (22%)
Injury and poisoning	800-999	49 (19.8%)	41 (20.2%)	26 (19.7%)	28 (22.8%)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	20 (8.1%)	11 (5.4%)	3 (2.3%)	6 (4.9%)

Output Table 21- Number and Causes of access to Hospitalization in the **year before cohort entry**

		Adalimumab (N=744)	Infliximab (N=990)	Golimumab (N=264)	Vedolizumab (N=468)
Description	ICD-9 code	N (%)	N (%)	N (%)	N (%)
Infectious and parasitic diseases	001-139	454 (61.0%)	575 (58.1%)	175 (66.3%)	280 (59.8%)
Neoplasms	139-239	4 (0.5%)	10 (1.0%)	7 (2.7%)	2 (0.4%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	29 (3.9%)	57 (5.8%)	4 (1.5%)	26 (5.6%)
Diseases of the blood and blood-forming organs	280-289	16 (2.2%)	31 (3.1%)	10 (3.8%)	17 (3.6%)
Mental disorders	290-319	4 (0.5%)	14 (1.4%)	-	1 (0.2%)
Diseases of the nervous system and sense organs	320-389	3 (0.4%)	10 (1.0%)	-	4 (0.9%)
Diseases of the circulatory system	390-459	18 (2.4%)	22 (2.2%)	4 (1.5%)	17 (3.6%)
Diseases of the respiratory system	460-519	8 (1.1%)	6 (0.6%)	6 (2.3%)	2 (0.4%)
Diseases of the digestive system	520-579	148 (19.9%)	223 (22.5%)	37 (14.0%)	94 (20.1%)
Diseases of the genitourinary system	580-629	17 (2.3%)	4 (0.4%)	5 (1.9%)	8 (1.7%)
Complications of pregnancy, childbirth, and the puerperium	630-679	5 (0.7%)	1 (0.1%)	-	-
Diseases of the skin and subcutaneous tissue	680-709	3 (0.4%)	-	-	1 (0.2%)
Diseases of the musculoskeletal system and connective tissue	710-739	7 (0.9%)	8 (0.8%)	6 (2.3%)	2 (0.4%)
Congenital Anomalies	740-759	2 (0.3%)	1 (0.1%)	-	1 (0.2%)
Certain Conditions Originating In The Perinatal Period	760-779	-	-	-	-
Symptoms, signs, and ill-defined conditions	780-799	-	8 (0.8%)	2 (0.8%)	-
Injury and poisoning	800-999	4 (0.5%)	1 (0.1%)	2 (0.8%)	4 (0.9%)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	22 (3.0%)	19 (1.9%)	6 (2.3%)	9 (1.9%)

Output Table 22 - Number and Causes of access to Hospitalization in the **one-year follow-up**

		Adalimumab (N=498)	Infliximab (N=666)	Golimumab (N=360)	Vedolizumab (N=360)
Description	ICD-9 code	N (%)	N (%)	N (%)	N (%)
Infectious and parasitic diseases	001-139	283 (56.8%)	361 (54.2%)	238 (66.1%)	215 (59.7%)
Neoplasms	139-239	5 (1.0%)	4 (0.6%)	5 (1.4%)	5 (1.4%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	25 (5.0%)	40 (6.0%)	9 (2.5%)	3 (0.8%)
Diseases of the blood and blood-forming organs	280-289	13 (2.6%)	16 (2.4%)	5 (1.4%)	17 (4.7%)
Mental disorders	290-319	-	9 (1.4%)	-	-
Diseases of the nervous system and sense organs	320-389	2 (0.4%)	10 (1.5%)	4 (1.1%)	1 (0.3%)
Diseases of the circulatory system	390-459	12 (2.4%)	30 (4.5%)	6 (1.7%)	18 (5.0%)
Diseases of the respiratory system	460-519	16 (3.2%)	4 (0.6%)	4 (1.1%)	2 (0.6%)
Diseases of the digestive system	520-579	92 (18.5%)	122 (18.3%)	55 (15.3%)	67 (18.6%)
Diseases of the genitourinary system	580-629	7 (1.4%)	12 (1.8%)	9 (2.5%)	8 (2.2%)
Complications of pregnancy, childbirth, and the puerperium	630-679	1 (0.2%)	-	1 (0.3%)	2 (0.6%)
Diseases of the skin and subcutaneous tissue	680-709	4 (0.8%)	4 (0.6%)	2 (0.6%)	-
Diseases of the musculoskeletal system and connective tissue	710-739	17 (3.4%)	6 (0.9%)	7 (1.9%)	4 (1.1%)
Congenital Anomalies	740-759	-	1 (0.2%)	-	1 (0.3%)
Certain Conditions Originating In The Perinatal Period	760-779	-	-	-	-
Symptoms, signs, and ill-defined conditions	780-799	1 (0.2%)	11 (1.7%)	3 (0.8%)	5 (1.4%)
Injury and poisoning	800-999	10 (2.0%)	11 (1.7%)	3 (0.8%)	1 (0.3%)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	10 (2.0%)	25 (3.8%)	9 (2.5%)	11 (3.1%)

Output Table 23- Number and Causes of access to Hospitalization in the **two-year follow-up**

		Adalimumab (N=1044)	Infliximab (N=1086)	Golimumab (N=696)	Vedolizumab (N=630)
Description	ICD-9 code	N (%)	N (%)	N (%)	N (%)
Infectious and parasitic diseases	001-139	584 (55.9%)	596 (54.9%)	439 (63.1%)	357 (56.7%)
Neoplasms	139-239	17 (1.6%)	10 (0.9%)	14 (2.0%)	6 (1.0%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240-279	37 (3.5%)	53 (4.9%)	18 (2.6%)	10 (1.6%)
Diseases of the blood and blood-forming organs	280-289	23 (2.2%)	26 (2.4%)	9 (1.3%)	25 (4.0%)
Mental disorders	290-319	5 (0.5%)	12 (1.1%)	2 (0.3%)	-
Diseases of the nervous system and sense organs	320-389	5 (0.5%)	16 (1.5%)	11 (1.6%)	2 (0.3%)
Diseases of the circulatory system	390-459	35 (3.4%)	43 (4.0%)	19 (2.7%)	35 (5.6%)
Diseases of the respiratory system	460-519	26 (2.5%)	6 (0.6%)	7 (1.0%)	2 (0.3%)
Diseases of the digestive system	520-579	183 (17.5%)	212 (19.5%)	101 (14.5%)	133 (21.1%)
Diseases of the genitourinary system	580-629	24 (2.3%)	16 (1.5%)	15 (2.2%)	14 (2.2%)
Complications of pregnancy, childbirth, and the puerperium	630-679	6 (0.6%)	2 (0.2%)	1 (0.1%)	2 (0.3%)
Diseases of the skin and subcutaneous tissue	680-709	5 (0.5%)	6 (0.6%)	3 (0.4%)	-
Diseases of the musculoskeletal system and connective tissue	710-739	31 (3.0%)	10 (0.9%)	15 (2.2%)	7 (1.1%)
Congenital Anomalies	740-759	-	1 (0.1%)	-	4 (0.6%)
Certain Conditions Originating In The Perinatal Period	760-779	-	-	-	-
Symptoms, signs, and ill-defined conditions	780-799	7 (0.7%)	17 (1.6%)	8 (1.1%)	10 (1.6%)
Injury and poisoning	800-999	21 (2.0)	12 (1.1%)	5 (0.7%)	5 (0.8%)
Supplementary classification of factors influencing health status and contact with health services	V01-V91	35 (3.4%)	48 (4.4%)	29 (4.2%)	18 (2.9%)

6.4 Research question 4

RQ4 aims at quantifying the economic impact among the different cohort considering both the overall direct health costs born to the RHS, considering the size of the different groups, both assessing per patient costs and the impact of the different cost components. The adalimumab cohort (n=239) implied an overall direct health cost to the RHS of more than 2.7 million Euro in the first year after treatment initiation. The overall cost for the cohort of 175 patients treated with infliximab was about 1.7 million Euro, about 1.6 million Euro for the 110 patients initiating golimumab and more than 1.8 million Euro for those treated with vedolizumab (n=107). For each cohort the overall direct health costs were largely driven by the cost of drugs. Indeed, for all cohorts, except for those treated with infliximab, costs associated with therapies accounted for 85% or more of the overall costs. While, the other cost components accounted for a small percentage of the overall economic burden. Among patients initiating Infliximab, 70% of overall cost in the first year after treatment initiation was associated with the treatment, 28% was related to hospitalizations (percentage that was about two times higher than in the other cohorts) and the remaining 2% of costs was associated with ED access or gastroenterological visits (**Table 24a**). The overall median costs per patient/year in the first year of treatment were higher in the vedolizumab and golimumab cohorts and lower among patients treated with adalimumab and infliximab. As observed before, the drugs accounted the large part of costs, with vedolizumab and golimumab cohorts showing the higher per patients/years costs associated with drugs (median value being 16,125€ per patient/year and 13,621€ per patient/year respectively), followed by adalimumab (10,228€ per patient/year) and infliximab (5,309€ per patient/year). For both ED accesses and hospitalizations, costs were almost null for the majority of patients in all cohorts. On the other side, median yearly costs associated with gastroenterological visits ranged between 59€ per patient (adalimumab) and 133€ per patient (vedolizumab) (**Table 24b**).

Analyzing the overall economic burden in the two years after cohort entry, the overall costs born to the RHS ranged from about 2.5 millions Euro (for the 100 patients initiating golimumab) to about 3.9 million Euro for the 181 patients treated with adalimumab. Similarly to the pattern of costs observed in the first year after cohort entry, also the two-year costs were mainly driven by drug costs (with percentage varying from

68% for infliximab to 83% for adalimumab), followed by costs associated with hospitalizations (representing a portion of the overall costs ranging from 16%, for adalimumab, to 30%, for infliximab), while ED accesses and specialist visits accounted for a small portion of the overall costs (**Table 25a**). Again, similarly to the first-year costs, median overall costs per patient were higher in the vedolizumab and golimumab cohorts (30,864€ and 26,269€, respectively), followed by adalimumab (22,152€) and infliximab (18,050€). Patients treated with vedolizumab and golimumab also showed the highest per patient costs associated with drugs (24,867€ per patient and 21,720€ per patient, respectively). While costs for ED visits and hospitalization were almost null for the majority of patients in the different cohorts, costs for specialist visits ranged from 155€ per patient (adalimumab) to 287€ per patient (vedolizumab) (**Table 25b**).

Analyzing median per patient costs according to year of cohort entry, **Table 26a** shows that total median costs per patient/year were about 14/15 thousand Euro as regard patients initiating adalimumab treatment from 2015 to 2017. The overall costs per patient/year was slightly lower for those entering the cohort in 2018 (about 11 thousand Euro), mainly because of the lowering of cost associated with the advanced treatment, probably induced also by the introduction of biosimilars. Finally, total direct health costs per patient/year was extremely low for those entering the cohort in 2019, as compared with patients entering the cohort in previous years. Indeed, for those initiating treatment with advanced therapy in 2019 a marked reduction in costs associated with the advanced therapy was observed. In the infliximab cohort, overall per patient costs in the first year following treatment initiation progressively decreased from a median cost of less than 14 thousand Euro for those entering the cohort in 2015 to less than 6 thousand Euro in 2018 and about 3.4 thousand Euro in 2019. Again, except for those entering the cohort in 2019 whose costs may be probably impacted by both the introduction of biosimilars and the pandemic, the decreasing pattern over years from cohort entry was mainly driven by a reduction in costs associated to infliximab, which was the main costs' component. Differently from the other cohorts, in the golimumab group, overall per patient costs slightly decreased over years of cohort entry and similarly for costs associated with advanced therapy. In this cohort just a slightly decrease of costs associated with other therapies and specialist visits was observed for those entering the cohort in 2019. In the vedolizumab cohort, overall per patient costs in the year following

treatment initiation were homogeneous among subjects entering the cohort from 2016 to 2019. In this group, we just observed a slight decrease over time of costs associated to both the advanced therapies and other treatments. Mean costs per patient over one-year follow-up and according to year of cohort entry are showed in Table 26b.

For what concerns costs in the two years following cohort entry, similar patterns emerged to that observed for the first year of treatment. In the adalimumab cohort, overall costs dropped down over years from the cohort entry and were extremely low for those entering the cohort in 2018, probably because of the effect of the introduction of biosimilars, and this pattern was driven by trend of costs associated with the advanced therapy; the other costs remained quite invariant over years. In the infliximab cohort, overall costs decrease was progressive over years, despite being more pronounced for those entering the cohort in 2018, and due to a reduction in costs associated with the advanced therapy. Among patients treated with golimumab overall costs were quite homogenous for those entering cohort from 2015 to 2017, while was lower for patients initiating treatment in 2018. This pattern was mainly driven by a decrease in costs of advanced therapy. Finally, among patients treated with vedolizumab, the analysis of per patient costs over the two years following treatment initiation highlighted that costs remained quite homogeneous over years, and similarly for the impact of the diverse costs components (**Table 27a**). Mean costs per patient over the two-year follow-up and according to year of cohort entry are showed in Table 27b.

Table 24a – Total direct costs in the **one-year follow up**

	Cost (€)			
	Adalimumab (n=239)	Infliximab (n=175)	Golimumab (n=110)	Vedolizumab (n=107)
Total cost	2,744,072	1,697,915	1,621,000	1,862,525
Drugs (%)	2,366,967 (86.3%)	1,182,502 (69.6%)	1,435,336 (88.5%)	1,580,497 (84.9%)
Emergency department access (%)	11,152 (0.4%)	7,435 (0.4%)	5,609 (0.3%)	5,689 (0.3%)
Hospitalization (%)	345,377 (12.6%)	476,415 (28.1%)	169,238 (10.4%)	261,332 (14.1%)
Specialist visits (gastroenterological) (%)	20,576 (0.7%)	31,563 (1.9%)	10,817 (0.8%)	15,006 (0.8%)

Table 24b –Direct costs per patient in the **one-year follow up**

	Cost (€)			
	Adalimumab (n=239)	Infliximab (n=175)	Golimumab (n=110)	Vedolizumab (n=107)
	Median cost per patient, [25th-75th percentile]			
Total costs	11,883 [4,364-15,760]	7,738 [3,989-13,716]	14,872 [11,989-17,448]	17,032 [13,410-20,345]
Drugs	10,228 [3,449-14,715]	5,309 [3,064-9,622]	13,621 [10,823-16,269]	16,125 [11,874-18,086]
Emergency department access	0 [0-0]	0 [0-0]	0 [0-43]	0 [0-43]
Hospitalization	0 [0-0]	0 [0-3,217]	0 [0-1,280]	0 [0-2,074]
Specialist visits (gastroenterological)	59 [0-147]	126 [38-210]	75 [28-148]	133 [42-191]
	Mean cost per patient, [min;max]			

Total costs	11,481 [393;37,612]	9,702 [395;34,916]	14,736 [1,146;29,300]	17,407 [3,541;42,277]
Drugs	9,903.6 [393; 28,652]	6,757 [380;29,063]	13,049 [1,013;29,225]	14,771 [2,038;25,267]
Emergency department access	46.7 [0;750]	42 [0;886]	51 [0;871]	53 [0;1,025]
Hospitalization	1,445.1 [0;31,954]	2,722 [0;31,628]	1,539 [0;17,853]	2,442 [0;27,615]
Specialist visits (gastroenterological)	86.1 [0;881]	180 [0;7,634]	98 [0;422]	140 [0;508]

Table 25a – Total direct costs in the **two-years follow up**

	Cost (€)			
	Adalimumab (n=181)	Infliximab (n=130)	Golimumab (n=100)	Vedolizumab (n=78)
Total cost	3,933,951	2,476,243	2,473,836	2,354,619
Drugs	3,267,170 (83.1%)	1,691,484 (68.3%)	2,025,028 (81.9%)	1,894,484 (80.5%)
Emergency department access	16,816 (0.4%)	11,087 (0.4%)	8,180 (0.3%)	6,988 (0.3%)
Hospitalization	616,028 (15.7%)	730,523 (29.5%)	420,547 (17.0%)	429,025 (18.2%)
Specialist visits (gastroenterological)	33,937 (0.9%)	43,149 (1.7%)	20,081 (0.8%)	24,122 (1.0%)

Table 25b –Direct costs per patient in the **two-years follow up**

	Cost (€)			
	Adalimumab (n=181)	Infliximab (n=130)	Golimumab (n=100)	Vedolizumab (n=78)
	Median cost per patient, [25th-75th percentile]			
Total costs	22,152 [13,655-27,945]	18,050 [9,824-25,420]	26,269 [19,167-29,972]	30,864 [24,344-35,589]
Drugs	18,474 [8,864-25,377]	10,435 [6,245-17,846]	21,720 [12,764-27,349]	24,867 [18,693-31,786]
Emergency department access	0 [0-115]	0 [0-87]	0 [0-81]	0 [0-70]
Hospitalization	0 [0-3,484]	0 [0-6,666]	0 [0-3,333]	0 [0-7,326]
Specialist visits (gastroenterological)	155 [44-297]	279 [135-389]	182 [62-315]	287 [118-458]
	Mean cost per patient, [min;max]			
Total costs	21,734.5 [1,038;55,543]	19,048 [450;51,776]	24,738 [1,273;57,030]	30,187 [3,541;56,713]
Drugs	18,051 [966;52,218]	13,011 [450;47,662]	20,250 [1,02;42,787]	24,288 [2,038;45,339]
Emergency department access	92.9 [0;855]	85 [0;1,043]	82 [0;871]	90 [0;1,219]

Hospitalization	3,403.5 [0;49,072]	5,619 [0;40,128]	4,205 [0;43,766]	5,500 [0;39,140]
Specialist visits (gastroenterological)	187.5 [0;1,126]	332 [0;7,745]	201 [0;547]	309 [0;958]

Table 26a – Median direct costs per patient in the **one-year follow up**, stratified by calendar years of cohort entry

	Cost (€)				
	2015	2016	2017	2018	2019
Median cost per patient, [25th-75th percentile]					
Adalimumab					
Total cost	15,325 [12,768-18,622]	14,144 [11,758-15,598]	14,080 [9,967-16,131]	10,682 [5,276-13,876]	2,921 [2,123-4,003]
Drugs	14,277 [9,087-15,984]	13,062 [7,472-15,062]	13,351 [9,429-14,983]	9,168 [4,483-12,049]	2,584 [1,767-3,283]
Advanced therapy	13,833 [8,749-15,945]	12,990 [6,173-14,984]	13,069 [9,194-14,925]	8,867 [4,304-11,585]	2,175 [1,611-2,487]
Other treatments	298 [64-881]	240 [12-566]	282 [60-707]	373 [45-889]	323 [38-754]
Emergency department access	0 [0-50]	0 [0-0]	0 [0-22]	0 [0-44]	0 [0-13]
Hospitalization	0 [0-1,545]	0 [0-2,402]	0 [0-0]	0 [0-0]	0 [0-0]
Specialist visits (gastroenterological)	97 [15-147]	51 [0-130]	45 [0-118]	45 [0-155]	30 [0-134]
Infliximab					
Total cost	13,716 [9,435-19,239]	12,353 [9,572-15,711]	8,408 [6,785-15,269]	5,776 [3,259-8,572]	3,493 [2,702-5,350]
Drugs	9,659 [5,176-13,367]	8,770 [7,261-12,097]	6,532 [5,089-10,324]	3,907 [2,546-5,952]	3,199 [2,408-3,922]
Advanced therapy	9,170 [4,653-12,013]	7,755 [6,895-11,370]	5,739 [4,488-9,524]	3,115 [1,917-4,784]	2,806 [1,664-3,469]
Other treatments	538 [263-1,162]	752 [291-1,191]	764 [470-1,301]	678 [120-948]	247 [62-832]
Emergency department access	0 [0-0]	0 [0-0]	0 [0-111]	0 [0-0]	0 [0-0]
Hospitalization	0 [0-6,720]	0 [0-3,333]	0 [0-1,715]	0 [0-2,465]	0 [0-0]
Specialist visits (gastroenterological)	154 [92-222]	124 [52-216]	132 [98-250]	113 [0-203]	114 [0-171]
Golimumab					
Total cost	14,698 [12,507-17,113]	16,919 [14,702-19,188]	15,944 [11,989-16,290]	12,557 [6,954-16,049]	11,893 [10,404-12,281]
Drugs	13,579 [8,663-15,795]	15,680 [12,432-17,060]	15,203 [11,566-16,260]	12,495 [5,272-15,595]	11,829 [10,404-13,265]
Advanced therapy	12,464 [8,550-14,537]	15,334 [11,300-16,552]	13,712 [11,170-15,344]	12,175 [5,036-14,443]	11,688 [9,816-12,449]
Other treatments	749 [142-1,499]	688 [447-1,257]	879 [364-1,268]	436 [81-1,591]	264 [44-587]
Emergency department access	0 [0-70]	0 [0-71]	0 [0-87]	0 [0-0]	0 [0-0]

	Cost (€)				
	2015	2016	2017	2018	2019
Hospitalization	0 [0-3,217]	0 [0-1,372]	0 [0-2,830]	0 [0-0]	0 [0-0]
Specialist visits (gastroenterological)	75 [0-207]	94 [60-148]	45 [30-60]	122 [30-154]	30 [0-106]
Vedolizumab					
Total costs	-	18,785 [15,168-22,071]	17,558 [14,629-20,345]	16,685 [12,639-21,419]	16,384 [13,491-18,210]
Drugs	-	16,277 [14,110-18,282]	17,182 [13,181-18,086]	14,232 [11,874-18,696]	14,592 [10,472-16,378]
Advanced therapy	-	14,110 [14,110-16,125]	16,125 [12,094-16,125]	14,110 [10,078-18,141]	14,110 [10,078-16,125]
Other treatments	-	950 [132-1,843]	1,056 [493-1,366]	747 [329-1,412]	523 [335-1,068]
Emergency department access	-	0 [0-49]	0 [0-0]	0 [0-22]	0 [0-61]
Hospitalization	-	0 [0-5,009]	0 [0-1,499]	0 [0-3,176]	0 [0-0]
Specialist visits (gastroenterological)	-	128 [74-253]	132 [69-191]	157 [36-252]	133 [24-167]

Table 26b – Mean direct costs in the **one-year follow up**, stratified by calendar years of cohort entry

	Cost (€)				
	2015	2016	2017	2018	2019
Mean cost per patient, [min;max]					
Adalimumab					
Total cost	15,146 [2,148;29,229]	14,460 [1,972;37,612]	13,878 [1,028;31,439]	11,137[1,932;33,369]	4,026 [393;27,574]
Drugs	13,320 [2,099;28,652]	12,218 [1,971;25,593]	12,947 [956;27,517]	9,306 [1,873;22,568]	2,864.1 [393;12,181]
Advanced therapy	12,831 [2,050;28,266]	11,669 [1,879;23,761]	12,389 [934;24717]	8,631 [923;21,711]	2,421 [356;10,333]
Other treatments	490 [0;2,897]	549 [0;6,031]	559 [0;2,799]	675 [0;3,256]	453 [0;1,848]
Emergency department access	42 [0;516]	43 [0;677]	32 [0;452]	44 [0;558]	66 [0;750]
Hospitalization	1,671 [0;15,327]	2,116 [0;31,954]	817 [0;11,898]	1,706 [0;25,577]	1,018[0;24,912]
Specialist visits (gastroenterological)	112 [15;881]	83 [0;453]	81 [0;438]	80 [0;288]	68 [0;265]
Infliximab					
Total cost	14,295 [2,637;29,309]	13,118 [1,493;25,512]	11,394 [508;31,727]	7,708 [395;34,916]	4,635 [682;20,222]
Drugs	9,834 [2,482;29,063]	9,823 [1,462;25,512]	8,375 [489;27,805]	4,376 [395;11,218]	3,508 [380;11,521]
Advanced therapy	9,061 [1,462;27,937]	9,051 [931;23,387]	7,491 [487;25,163]	3,621 [300;10,975]	3,020 [359;10,068]
Other treatments	774 [0;2,848]	772 [1;2,125]	884 [0;2,642]	755 [3;4,978]	487 [0;1,784]
Emergency department access	30 [0;517]	29 [0;337]	76 [0;534]	35 [0;886]	45 [0;695]
Hospitalization	4,048 [0;21,699]	3,122 [0;17,316]	2,767 [0;26,559]	3,178 [0;31,628]	971 [0;16,491]
Specialist visits (gastroenterological)	1382 [0;7,634]	144 [0;327]	176 [0;442]	120 [0;390]	111 [0;389]
Golimumab					
Total cost	15,253 [3,425;29,300]	16,580 [3,768;26,955]	14,771 [8,919;23,643]	11,475 [1,146;17,988]	11,675 [7,330;13,832]
Drugs	12,888 [3,271;29,225]	14,360 [3,768;20,815]	13,681 [5,552;20,172]	10,832 [1,013;17,859]	11,531 [7,330;13,580]
Advanced therapy	11,989 [3,115;29,076]	13,453 [3,115;19,682]	12,775 [4,928;18,171]	9,994 [1,007;16,268]	10,924 [4,822;13,267]
Other treatments	900 [27;3,115]	907 [5;2,265]	906 [0;2032]	838 [6;2,552]	607 [0;2,508]
Emergency department access	66 [0;871]	51 [0;451]	69 [0;408]	6 [0;44]	37 [0;343]

	Cost (€)				
	2015	2016	2017	2018	2019
Hospitalization	2,189 [0;17,434]	2,056 [0;17,853]	963 [0;3,333]	524 [0;5,739]	52 [0;520]
Specialist visits (gastroenterological)	110 [0;422]	113 [0;413]	58 [0;189]	114 [0;315]	56 [0;162]
Vedolizumab					
Total costs	-	19,347 [12,927;28,340]	17,939 [3,541;36,042]	17,395 [6,149;42,277]	15,801 [6,477;25,245]
Drugs	-	14,674 [3,797;24,646]	15,542 [2,038;25,267]	14,977 [6,047;22,644]	13,642 [2,399;22,880]
Advanced therapy	-	13,596 [3,665;22,172]	14,515 [2,016;24,188]	14,004 [6,047;22,172]	12,919 [2,016;22,150]
Other treatments	-	1,077 [0;2,492]	1,027 [18;2,909]	973 [0;3,246]	723 [0;2,451]
Emergency department access	-	46 [0;322]	54 [0;1,025]	47 [0;608]	55 [0;269]
Hospitalization	-	4,451 [0;24,220]	2,197 [0;19,952]	2,219 [0;27,615]	1,993 [0;16,912]
Specialist visits (gastroenterological)	-	163 [0;393]	146 [0;508]	151 [0;357]	111 [0;434]

Table 27a – Median direct costs per patient in the **two-year follow up**, stratified by calendar years of cohort entry

	Cost (€)			
	2015	2016	2017	2018
Median cost per patient, [25th-75 th percentile]				
Adalimumab				
Total cost	25,996 [19,099-29,656]	23,700 [19,574-27,890]	20,436 [14,894-25,956]	13,656 [8,999-19,393]
Drugs	23,290 [12,541-28,256]	22,638 [10,300-26,581]	18,391 [11,516-22,630]	11,434 [6,965-14,213]
Advanced therapy	22,370 [12,024-27,973]	22,376 [6,173-25,445]	17,791 [9,335-21,799]	10,846 [5,933-14,040]
Other treatments	429 [123-1,206]	453 [65-979]	680 [91-1,687]	837 [105-2,202]
Emergency department access	11 [0-100]	0 [0-77]	0 [0-154]	11 [0-147]
Hospitalization	0 [0-3,333]	0 [0-3,741]	0 [0-5,744]	0 [0-3,236]
Specialist visits (gastroenterological)	181 [82-321]	88 [2-234]	159 [30-286]	147 [57-283]
Infliximab				
Total cost	21,494 [18,196-29,165]	20,810 [16,683-29,412]	14,755 [11,144-25,420]	9,443 [6,287-16,908]
Drugs	15,224 [8,817-21,100]	16,634 [9,509-20,940]	10,548 [6,825-16,144]	6,378 [4,384-9,470]
Advanced therapy	14,269 [8,283-18,586]	15,542 [8,898-20,021]	8,770 [6,355-15,305]	4,967 [2,622-7,310]
Other treatments	986 [365-1,963]	1,371 [524-2,075]	1,257 [839-2,313]	1,230 [484-1,875]
Emergency department access	0 [0-84]	0 [0-44]	22 [0-235]	0 [0-44]
Hospitalization	1,000 [0-11,428]	1,625 [0-6,930]	1,148 [0-6,320]	0 [0-3,333]
Specialist visits (gastroenterological)	278 [195-350]	285 [146-407]	309 [193-427]	211 [0-351]
Golimumab				
Total cost	26,457 [21,611-30,662]	28,454 [22,208-32,482]	24,056 [22,608-28,782]	18,845 [10,232-23,979]
Drugs	21,011 [12,016-26,821]	24,586 [14,451-29,036]	21,890 [13,435-27,464]	18,458 [5,396-23,553]
Advanced therapy	17,668 [10,383-24,776]	23,227 [13,498-28,507]	21,147 [13,435-25,282]	16,466 [5,036-23,282]

	Cost (€)			
	2015	2016	2017	2018
Other treatments	1,369 [289-2,670]	1,360 [751-2,579]	1,718 [602-2,063]	1,344 [271-2,927]
Emergency department access	44 [0-126]	0 [0-105]	0 [0-87]	0 [0-44]
Hospitalization	0 [0-5,544]	0 [0-3,236]	0 [0-3,333]	0 [0;13,391-1,280]
Specialist visits (gastroenterological)	156 [0-316]	202 [74-279]	217 [77-368]	154 [62-386]
Vedolizumab				
Total costs	-	35,807 [31,053-39,420]	29,351 [23,215-33,501]	30,857 [25,000-34,593]
Drugs	-	23,360 [14,179-30,918]	24,675 [15,010-31,450]	25,896 [19,653-33,301]
Advanced therapy	-	21,164 [14,110-30,235]	22,627 [13,966-28,220]	24,188 [18,141-30,235]
Other treatments	-	1,377 [139-2,567]	1,967 [659-2,657]	1,465 [448-2,636]
Emergency department access	-	46 [0-217]	0 [0-40]	22 [0-51]
Hospitalization	-	0 [0-18,684]	0 [0-5,733]	0 [0-5,690]
Specialist visits (gastroenterological)	-	318 [74-386]	228 [122-431]	370 [102-550]

Table 27b – Mean direct costs per patient in the **two-year follow up**, stratified by calendar years of cohort entry

	Cost (€)			
	2015	2016	2017	2018
	Mean cost per patient, [min;max]			
Adalimumab				
Total cost	25,114 [2,229;55,543]	23,360 [2,140;43,703]	22,200 [1,038;51,404]	14,897 [1,989;33,812]
Drugs	21,041 [2,166;52,218]	19,919 [2,079;40,408]	18,337 [966;47,305]	11,755 [1,930;29,336]
Advanced therapy	20,111 [2,050;51,816]	18,863 [1,879;40,388]	17,155 [934;42,858]	10,517 [923;25,131]
Other treatments	930 [0;4,538]	1,057 [0;13,548]	1,183 [0;4,970]	1,238 [3;4,856]
Emergency department access	83 [0;632]	107 [0;855]	86 [0;505]	102 [0;605]
Hospitalization	3,777 [0;49,072]	3,184 [0;36,638]	3,589 [0;26,934]	2,860 [0;25,748]
Specialist visits (gastroenterological)	214 [0;1,126]	150 [0;710]	188 [0;615]	181 [0;560]
Infliximab				
Total cost	23,735 [8,739;44,444]	22,299 [8,146;41,595]	19,199 [508;51,776]	12,877 [450;39,544]
Drugs	15,878 [3,220;43,721]	17,121 [1,462;40,812]	13,062 [489;47,662]	7,764 [450;25,568]
Advanced therapy	14,576 [1,462;41,599]	15,645 [931;36,399]	11,457 [487;43,304]	6,292 [230;25,085]
Other treatments	1,303 [0;4,613]	1,475 [1;4,574]	1,605 [0;4,358]	1,472 [8;9,060]
Emergency department access	83 [0;700]	40 [0;337]	128 [0;594]	91 [0;1,043]
Hospitalization	7,287 [0;40,218]	4,831 [0;29,426]	5,687 [0;35,204]	4,791 [0;31,628]
Specialist visits (gastroenterological)	487 [0;7,745]	307 [0;783]	322 [0;748]	231 [0;686]
Golimumab				
Total cost	25,896 [3,619;47,307]	26,986 [7,605;57,030]	24,441 [10,419;35,637]	17,429 [1,273;30,114]
Drugs	19,807 [3,295;42,787]	22,535 [4,369;39,993]	20,837 [9,602;30,029]	15,594 [1,026;29,921]
Advanced therapy	18,031 [3,115;42,575]	20,744 [3,115;35,033]	19,261 [8,447;28,311]	14,146 [1,007;26,995]

	Cost (€)			
	2015	2016	2017	2018
Other treatments	1,776 [39;9,826]	1,790 [10;5,276]	1,576 [0;3,644]	1,449 [19;4,306]
Emergency department access	119 [0;871]	61 [0;451]	106 [0;855]	13 [0;65]
Hospitalization	5,786 [0;31,748]	4,190 [0;43,766]	3,274 [0;23,757]	1,608 [0;13,391]
Specialist visits (gastroenterological)	184 [0;532]	200 [0;487]	224 [0;511]	214 [0;547]
Vedolizumab				
Total costs	-	34,590 [16,908;50,071]	28,224 [3,541;50,247]	30,596 [10,002;56,714]
Drugs	-	21,673 [3,804;38,956]	23,717 [2,038;45,339]	25,427 [6,054;43,212]
Advanced therapy	-	20,075 [3,665;34,267]	21,844 [2,016;44,345]	24,733 [6,047;42,136]
Other treatments	-	1,598 [0;4,689]	1,873 [22;4,812]	1,694 [7;5,784]
Emergency department access	-	102 [0;322]	72 [0;1,219]	107 [0;864]
Hospitalization	-	12,504 [0;39,140]	4,137 [0;32,063]	3,738 [0;27,615]
Specialist visits (gastroenterological)	-	324 [0;729]	297 [0;958]	312 [0;943]

7 Conclusions

The advanced treatments of UC (adalimumab, infliximab, golimumab, vedolizumab) in Tuscany (Italy) appears to be substantially in line with the guidelines recommending the use of these drugs in the second and third line of treatment. Adalimumab is the most widely used drug as a first-line advanced treatment. The use of golimumab has been gradually decreasing over the years. The treatment of UC with tofacitinib was authorized in Italy only in late 2019. For this reason, there are no subjects with UC identifiable with the inclusion criteria in the Tuscan population.

In the analyzed cohorts the patients show a rather high adherence. This probably reflects the inclusion criteria (hospital discharge records) which prompt the identification of subjects with clinically relevant conditions and who probably require continued therapy, sometimes with increased doses.

Persistence in therapy is particularly high for each index drug with few subjects switching to other advanced therapies in the first and second year of treatment. This is especially true for vedolizumab-treated patients who remain 90% free from other advanced therapies after two years of follow-up. This result must be interpreted in light of the fact that vedolizumab was introduced into clinical use during the observation period and it is possible that, at least in the early years, it was used in selected subjects.

The consumption of other drugs of interest is quite stable over time with mesalazine, corticosteroids and antibiotics being among the most consumed drugs, more or less similarly in all cohorts of users. The trend of antibiotic consumption appears to be linked with the occurrence of infections that are frequently reported in hospital discharge records.

If we consider access to emergency rooms, hospitalizations and specialist visits, there were no major differences between the cohorts of users of advanced therapies. Typically, patients on adalimumab appear to have longer time-free from ED or hospitalization than those receiving the other advanced treatments.

The direct costs to the healthcare system in the first year of treatment with each of these drugs range from € 13,000 for infliximab to € 28,000 for vedolizumab per patient and are largely driven by the cost of the drug. Over the years there is a progressive reduction in costs in the first year of use for infliximab and mainly for adalimumab. This is certainly linked to the introduction and subsequent diffusion of biosimilar medicinal products for these drugs during the observation period.

For those enrolled in 2019 and followed for one year and those enrolled in 2018 and followed for two years, we expected to observe some differences related to the spread of the COVID-19 pandemic that may have limited access to treatment. However, no major differences have been actually observed and those that have been observed probably depend to a large extent on other causes.

8 References

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