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Failed Initial Tumor Necrosis Inhibitor (Tnfi) Therapy – What Next For Rheumatoid Arthritis Patients?

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FAILED INITIAL TUMOR NECROSIS INHIBITOR (TNFI) THERAPY – WHAT NEXT FOR RHEUMATOID ARTHRITIS PATIENTS?

by

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DEDICATION

To Alter & Hannah Karpes

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FAILED INITIAL TUMOR NECROSIS INHIBITOR (TNFI) THERAPY – WHAT NEXT FOR RHEUMATOID ARTHRITIS PATIENTS?

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Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints affecting over 1.3 million Americans with annual societal costs estimated at $39.2 billion, rising faster than medical inflation. Therapy with tumor necrosis factor inhibitors (TNFi) has greatly improved the management of patients with rheumatoid RA; however, substantial numbers of patients do not experience an adequate response to these drugs, necessitating a change in treatment regimen. There are two basic approaches for TNFi failure: cycling (switching to a second TNFi) or swapping (to a drug with another mechanism of action) but the choice is controversial due to questions of comparative efficacy and pervasive resource constraints.

The initial goal of this study was to follow the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and systematically review the methodology of decision analyses aimed at determining the most cost-effective sequence of treatment for refractory RA in order to gauge best modeling practices and sources of disagreement in terms of techniques and parameters. The second goal was to analyze the Truven Health Analytics MarketScan® Databases to obtain real-world estimates for cost and drug survival parameters for all ten targeted drugs. Ultimately, the aim was to apply the

lessons learned from the systematic review and the estimates calculated from claims data in order to develop an original decision analysis model that will assist physicians and patients in determining the most cost-effective course of care.

Seven publication met the criteria for inclusion into the systematic review. They had a largely homogenous model structure and their efficacy estimates were from the same set of randomized clinical trials. Reporting quality was fair and the median ICE for the swapping strategy was $70,332/QALY.

The claims analysis demonstrated that 63% of patients cycle to a second TNFi but those who swap to a non-TNFi drug are more likely to persist on treatment, even after controlling for covariates. There were no differences in time to discontinuation for subsequent lines of drugs. While non-TNFi drugs seem to be more effective, they are more costly. Adalimumab and abatacept are the most common second-line TNFi and non-TNFi respectively.

Lastly, we built a Markov microsimulation model based on the Truven cohort and conclude that swapping to a non-TNFi is likely to be cost-effective at a $100,000/QALY threshold across a variety of scenarios. Probabilistic sensitivity analysis estimates that the basecase has an 80% probability of being cost-effective at $100,000/QALY. Our results calibrate well with those seen in the systematic review and have the advantage of being based on long-term follow up of a large real-world cohort.

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Literature Review

The overall goal of RA therapy is to "treat to target" i.e. to remission or low disease activity. The most current treatment guidelines, as published by the ACR (1), recommend beginning with methotrexate (MTX) monotherapy, moving to combination conventional synthetic disease modifying antirheumatic drug (csDMARDs) therapy or a targeted drug (preferably together with MTX) and then adding low-dose corticosteroids. While there is no recommendation to use a TNFi versus a biological with another mechanism of action or tofacitinib (a targeted synthetic DMARD (tsDMARD)), most clinicians begin with a TNFi.

For patients who fail their initial TNFi and are not on concurrent csDMARDs, the ACR strongly recommends adding combination therapy with one or two conventional synthetic DMARDs. No double-blind randomized controlled study has directly addressed whether to use another TNFi versus a non-TNFi biologic for persons failing their first TNFi while on combination therapy. The results from observational studies are mixed and seem to indicate greater clinical improvement for non-TNFi drugs but possibly more serious infections. No study has compared TNFi to non-TNFi to tofacitinib. Thus, based on panelists' expertise, the ACR conditionally recommend swapping to a non-TNFi biological (1).

The EULAR recommendations are similarly equivocal, making no distinction between a second TNFi and different classes of biologic agents (2).

If a patient has failed to more than one TNFi, indirect observational studies appear to show greater effectiveness for non-TNFi's (with or without MTX) in terms of achieving the EULAR "good response" criteria but no difference in the DAS28 nor has a difference been shown in terms of serious infections.

Effectiveness

Switching between TNFi can be effective as, despite belonging to the same class, they have differences in formulation, molecular structure, pharmacokinetics and the induction of antibodies thereby inhibiting the inflammatory effects of tumor necrosis factor alpha in different ways. Targeted drugs with other mechanisms of action block the inflammatory effects of cytokines such as interleukin-1 (anakinra (ANA)), interleukin-6 (tocilizumab (TCZ)). They inhibit T-cells (abatacept (ABA)) or deplete B-cells (rituximab (RTX)). The drugs also differ in their methods of administration (injected, infused or ingested) and dosing schedules (from daily to six-monthly) which may contribute to differences in effectiveness, adherence, persistence, switching and dose escalation. That said, when restricting their analysis to patients starting their second targeted treatment after 2005, Ramiro et al (3) found no difference between the eight (their study excluded tofacitinib and anakinra) survival curves (p=0.239).

Randomized controlled trials (RCTs) show that both TNFi (OPPOSITE – infliximab (IFX) (4) GO-AFTER – golimumab (GOL) (5), CERT-001 – certolizumab (CTZ) (6)) and non-TNFi (ATTAIN – abatacept (7), REFLEX – rituximab (8), RADIATE – tocilizumab (9) and tofacitinib (TOF) (10)) are superior to placebo for patients who have failed their first

TNFi, with non-TNFi drugs appearing to be more effective than a second TNFi. Safety profiles are similar. Salliot et al (11) performed an indirect comparison of four of these RCTs (REFLEX, ATTAIN, RADIATE, GO-AFTER) as well as DANCER (rituximab) and report no significant difference between rituximab, tocilizumab, abatacept and golimumab. Schoels et al (12) arrived at a similar conclusion after performing an indirect pairwise meta-analysis of REFLEX, ATTAIN, RADIATE and GO-AFTER.

Cycling strategies

Most studies comparing the different TNFi's have found no difference between them (13, 14), indeed, one Veterans Administration study even found no added benefit to cycling to a new TNFi compared to restarting the initial drug after a gap of three months or longer (15). However there does appear to be a slight advantage to etanercept (ETN) according to the ARTIS study, based on the Swedish national registry (16) as well as a study based on the LOHREN registry in northern Italy (17). Similarly, in the US, Ramiro et al (3) found a significant difference, when comparing the survival curves of the three earliest TNFi ($p=0.044$) with infliximab and etanercept having an advantage over adalimumab (ADA).

Swapping strategies

The ROC trial (18), was a pragmatic, open-label, randomized controlled trial (RCT) comparing cycling to swapping in 300 participants. It included a sub-analysis evaluating the difference in disease response among abatacept, rituximab and tocilizumab and found no significant difference between them. Similarly, the discontinued SWITCH trial found similar improvement in outcomes for patients receiving rituximab and abatacept (19). However, a

network meta-analysis of randomized clinical trials in RA patients who had inadequate response to TNFi found that tocilizumab 8mg performed best in terms of ACR20 response rate and safety, followed by rituximab, abatacept and tofacitinib (20). This result has not been reflected in reports from the few observational studies that have compared outcomes between non-TNFi drugs as second-line targeted therapy (rituximab versus abatacept (21), rituximab versus tocilizumab (22) and abatacept versus tocilizumab(23)) which have not shown clear differences between them.

Cycling versus Swapping

The ROC trial (18), mentioned above, the only completed RCT found that directly compares cycling (to infliximab etanercept, adalimumab) versus swapping (to abatacept, rituximab or tocilizumab) and it found that significantly more patients receiving a non-TNFi drug achieved a good or moderate response at 24 weeks. There appears to be a trend towards more adverse events in the swapping group but other than for serious adverse events ($p=0.1$) the statistical significance was not reported. The British SWITCH open-label RCT was discontinued due to slow enrolment. Based on the 122 randomized patients, they could not conclusively determine a clinical difference between rituximab and a second TNFi (19). Lastly, an analysis of 32 RCTs using meta-regression determined that cycling results in better clinical response (24). Ramiro et al (3) report a somewhat lower discontinuation rate for TNFi as second line versus non-TNFi but this was not significant when restricted to patients beginning treatment after 2005.

Most comparative observational studies comparing rituximab to TNFi's in patients who have failed their first tumor necrosis factor inhibitor conclude that rituximab is more effective (22, 25-33). Gomez-Reino et al (31) believe that at least part of their result can be attributed to the poorer response they observed in patients cycling to adalimumab or infliximab compared to etanercept or rituximab. The SWITCH-RA study (29) did however go on to note that patients receiving rituximab had, on average, higher disease activity and had discontinued their previous TNFI due to inefficacy rather than adverse events. Finckh et al (26, 32) found significantly better improvement in disease activity among those rituximab patients who switched due to inadequate response, and no difference between RTX and TNFi if the switch was for any other reason. Rubbert-Roth et al (27) performed a prospective observational study of 728 patients and found significant improvement over six months for seropositive patients (anti-CCP+ n=559) swapping to rituximab versus cycling to a second TNFi. No difference was found for seronegative patients (anti-CCP- n=169).

Favalli et al (14) found that, regardless of the reason for the switch, those swapping to abatacept, rituximab or tocilizumab had better retention rates, with no significant difference between the three agents, a Dutch cohort study similarly reports higher effectiveness when swapping to non-TNFi's (34) whereas Ramiro et al (35) report no significant difference in discontinuation rates between cyclers and swappers. Strehblow et al (36) report a trend of longer survival on anakinra compared to TNFi but this did not reach statistical significance and Yoshida et al (37) report no significant difference between tocilizumab and TNFi's as second line treatment. The latter two studies were limited by small sample size (49 – 85 patients). Rotar and Tomsic (22, 33) found that tocilizumab is superior to TNFi's. Lastly,

Meissner (38) found that abatacept as second-line treatment had lower rates of switching than ADA, ETN and IFX as did Rosenblatt et al (39), who calculated that patients swapping from first-line TNFi to abatacept had a third of the odds of failing compared to those cycling to another TNFi. Schabert et al (40) report a more favorable efficacy profile for abatacept compared to adalimumab, etanercept and infliximab. In the same vein, both Du Pan et al and Elkin et al show favorable results for swapping versus cycling (41, 42). However, Harrold et al (43) found no difference between a second TNFi and abatacept. Only Studenic et al (44) report a higher retention rate for TNFi's compared to non-TNFi drugs for the second through fourth line of treatment. Virkki et al (45) distinguished between reasons for initial failure and found that switching to a second TNFi would be most beneficial to those experiencing secondary failure. Wakabayashi et al (46) report no significant difference in efficacy between tocilizumab and etanercept in 38 Japanese patients who had failed to respond to infliximab.

The most comprehensive studies compared survival times across eight or nine second-line drugs using Thomson Reuters MarketScan® Research Databases: the earlier study (47) (n=3049) calculated that etanercept and rituximab had the lowest switch rates and infliximab had the highest while the updated study (48) (n=6841) found highest persistence for rituximab and lowest for adalimumab with no significant differences between the other agents. The latter was the only study to include certolizumab pegol and no study has been found comparing tofacitinib as a second line targeted therapy.

In their systematic review of four studies and 41 abstracts looking at rituximab, abatacept, adalimumab, etanercept and infliximab as second line biologics, Moots et al (49)

conclude that significant benefit can be derived from all of them, qualifying their remarks by stating a need to possibly stratify patients according to biomarkers (such as seropositivity) in order to optimize therapy for specific subgroups.

Particularly when looking at observational studies, one needs to asses results in terms of regression to the mean: because the change to a new medication is triggered by an increase in disease activity, regardless of treatment, or lack thereof, any subsequent measure of disease activity is likely to reflect the patient's average disease activity which can be incorrectly attributed to drug efficacy.

That said, the evidence appears skewed in favor of the swapping strategy but, despite this, US patients tend to cycle to another TNFi rather than swap (3, 30, 50, 51) to a drug with another mechanism of action although this trend does appear to be changing (3, 52).

Table 1: Comparative effectiveness of second-line biologic drugs

Comparators	Reference	Data source	More efficacious
		TNFi versus TNFi	
IFX vs. ETN vs. ADA	Ramiro (3)	US prospective cohort	IFX, ETN
	Chatzidionysiou (16)	Swedish Registry	ETN
	Caporali (17)	Northern Italy registry	ETN
	Favalli (14)	Italian retrospective cohort	No difference

Comparators	Reference	Data source	More efficacious
IFX vs. ETN vs. ADA vs. GOL vs. CTZ	Greenberg (13)	US Registry	No difference
non-TNFi vs. non-TNFi			
ADA vs. RTX vs. ABA	Gottenberg (18)	Pragmatic RCT	No difference
RTX vs. ABA	Barnabe (21)	Canadian retrospective cohort	No difference
RTX vs. TCZ	Rotar (22)	Slovenian registry	RTX (NS)
TCZ vs. ABA	Kume (53, 54)	Japanese RCT	TCZ
TCZ vs. ABA	Leffers (23)	Dutch registry	No difference
TCZ vs. RTX vs. ABA vs. TOF	Lee (20)	Meta-analysis	TCZ
RTX vs ABA	Brown (19)	British RCT	RTX
TNFi vs non-TNFi			
Cycle vs. swap	Favalli (14)	Italian retrospective cohort	Swap
	Rotar (33)	Slovenian registry	Swap
	Brickmann (34)	Dutch retrospective cohort	Swap
	Du Pan (41)	Swiss registry	Swap
	Elkin (42)	US retrospective cohort	Swap
	Studenic (44)	Austrian retrospective cohort	Cycle
	Gottenberg (18)	French RCT	No difference
	Ramiro (3)	US prospective cohort	No difference
Cycle vs. RTX	Soliman (25)	British registry	RTX
	Rotar (22)	Slovenian registry	RTX
	Finck (26, 32)	Prospective cohort within Swiss registry	RTX
	Rubbert-Roth (27)	Global prospective cohort	RTX
	Chatzidionysiou (28)	Stockholm registry	RTX
	Emery (29)	Global prospective cohort	RTX

Comparators	Reference	Data source	More efficacious
	Harrold (30)	US registry	RTX
	Gomez-Reino (31)	Spanish prospective cohort	RTX
	Brown (19)	British RCT	No difference
Cycle vs. anakinra	Strehblow (36)	Prospective cohort	Anakinra - NS
Cycle vs. TCZ	Rotar (22)	Slovenian registry	TCZ
	Yoshida (37)	Japanese registry	No difference
Cycle vs. ABA	Rosenblatt (39)	US claims data	ABA
	Harrold (43)	Retrospective cohort	No difference
	Meissner (38)	US claims data	ABA
TCZ vs. ETN	Wakabayashi (46)	Japanese retrospective cohort	No difference
All vs. all	Ramiro (3)	US prospective cohort	TNFi – pre 2005
	Johnston (67)	US claims data	ETN, RTX best IFX worst
	Johnston (68)	US claims data	RTX best, ADA worst

Cost

Very few studies were found comparing costs of second line biological drugs for RA. Among the first three tumor necrosis factor inhibitors (ETN, IFX, ADA), etanercept appears to be consistently associated with the lowest drug cost per treated patient as well as the lowest all-cause healthcare costs. Infliximab is the most expensive (40, 55-57). This result must be treated with caution as only one study specifically looked at second line treatment, the others differentiated between new and continuing patients with no information on the treatment history of the continuing patients. Johnston et al (58) specifically compared first and second line treatment of sub-cutaneous (SC) targeted drugs and observed the lowest

costs for abatacept. Another paper by the same authors compared changes from baseline and concluded that while patients receiving abatacept as second line treatment were sicker than those receiving etanercept or adalimumab, their relative increase in healthcare costs was the lowest (59). When comparing among second line infused drugs, tocilizumab had significantly lower per person, per month (PPPM) and all-cause healthcare costs than abatacept and infliximab (60).

Overall, cycling appears to be a cheaper strategy than swapping. Patients who swap to non-TNFi drugs tend to be older, with more comorbidities and higher steroid use, but even after controlling for baseline characteristics, swapping results in approximately 35% higher annual all-cause medical costs (61) with 49-63% of the difference being attributed to the cost of the drug (51). This latter is attributed to the intravenous (IV) route of administration associated with many non-TNFi requiring office visits, facility fees and administration costs (51, 61, 62) . No significant difference was found in emergency department or inpatient visits (51).

Table 1: Comparative cost of second-line targeted drugs

Comparators	Paper	Source	Least costly
IFX vs. ETN vs. ADA	Schabert (40, 56, 57)	US claims data	ETN
	Harrison (55)	US claims data	ETN
SC drugs (ADA vs. ETN vs. ABA)	Johnston (58, 59)	US claims data	ABA
IV drugs (IFX vs. ABA vs. TCZ)	Johnston (60)	US claims data	TCZ
Cycle vs swap	Zhou (51)	US claims data	Cycle
	McBride (61)	US claims data	Cycle
	Baser (62)	US claims data	Cycle

Cost effectiveness

Joensuu et al (63) reviewed cost-utility analyses of biologics in RA across five categories of patients, one of which included studies that compared biologics in patients with an inadequate response to TNFi's. Four studies met their inclusion criteria all of which compared rituximab to one or more TNFi's (adalimumab, etanercept and/or infliximab), one also included abatacept as a treatment option. All of them are European studies. Three studies (64-66) included indirect costs while Merkesdal et al (64) and Kielhorn et al (67) were the only analyses of treatment sequences although in both cases the only difference in the sequences presented was the inclusion of rituximab as the first biological after initial TNFi failure in one arm. The analyses including rituximab conclude that RTX compared to TNF's is either cost-effective at the €30,000 incremental cost effectiveness ratio (ICER) threshold or

is the dominant option (cheaper and more effective). The ICERs for abatacept ranged from €47,663 to over 1.2 million euros. No clear best choice emerges among the three TNFi's included in the models.

Sullivan et al (68) conclude from their review of 15 articles that cycling to a second TNFi is less likely to be cost-effective whereas swapping to abatacept or rituximab results in an ICER below willingness to pay thresholds and may even be cost-saving.

An initial literature search revealed a further five cost-utility (19, 65, 69-71) and four cost-effectiveness (72-75) analyses all comparing treatment arms consisting of TNFi's, abatacept and/or rituximab. Three studies were performed in Central America, the rest are based on European populations. The overall conclusion appears to be that swapping to a non-TNFi biological is more cost-effective than cycling to a second TNFi. Four cost-utility analyses (CUA) favored rituximab whereas half of the six cost-effectiveness analyses (CEA) did so. The incomplete SWITCH study concluded that an alternative TNFi might be cost-effective when compared to rituximab but that abatacept is unlikely to be cost-effective when compared to TNFi (19). Given the substantial uncertainty inherent in assumptions about disease progression under the different treatment options complicated by the diverse populations of the nine countries represented and the different modelling assumptions and structures used, it is not possible to reach an unequivocal conclusion.

Table 2: Comparative cost-utility of second-line targeted drugs

Drug	Comparator	Study	Country	ICER
RTX	TNFi	Brodszky (65)	Hungary	RTX dominant
	TNFi ⇨TNFi	Carlos (69)	Mexico	RTX dominant
	TNFi	Diamantopolous (70)	Netherlands	RTX dominant
	ABA	Diamantopolous (70)	Netherlands	RTX dominant
	TNFi	Manders (71)	Netherlands	RTX dominant
	TNFi	Brown (76)	United Kingdom	TNFi: £5,332/QALY
ABA	TNFi	Brown (76)	United Kingdom	ABA: £253,967/QALY

Table 3: Comparative cost-effectiveness of second-line targeted drugs

Drug	Comparator	Study	Country	Result
RTX	TNFi	Carlos (73)	Costa Rica	RTX: lowest cost/ACR70
	TNFi	Carlos (75)	Mexico	RTX: lowest cost/ACR70
	TNFi	Ryazhenov (74)	Russia	RTX: lowest cost/unit DAS reduction
	ABA	Ryazhenov (74)	Russia	RTX: lowest cost/unit DAS reduction
ABA (3^{rd} line)	RTX	Emery (72)	UK	£8/day in LDAS*

* LDAS: low disease activity state

Public Health Significance

Annual health care costs in the United States have exceeded the $3 trillion mark accounting for 17.5% of Gross National Product in 2014 (77) which is approximately double the OECD per capita average. Americans are paying more for health care but this is not reflected in superior health outcomes. One of the primary goals of the Patient Protection and Affordable Care Act (ACA) of 2010 was to improve the efficiency of the US health care system. The increase in the number of insured individuals as well as the overall aging of the population mean not only that more people will have access to targeted disease-modifying anti-rheumatic drugs, but they will be needing them for longer. There is no consensus on the most effective second line treatment, and a paucity of information on the most cost-effective. The uncertainty of treatment success, coupled with risk and high expense make these therapies an important target for economic evaluations as it is important for patients that their physicians have guidance on the most cost-effective options for controlling their disease. This study aims to provide such a tool by providing a systematic synthesis of the relative costs and benefits of alternative rheumatoid arthritis treatments for patients who have failed their initial TNFi agent.

Hypothesis, Research Question, Specific Aims or Objectives

The essential purpose of this research project is to build a cost-utility model that will assist physicians and rheumatoid arthritis patients in treatment selection after failing their initial TNFi. In order to be relevant and valid, the model needs to be based on best decision analysis practices. To that end a systematic methodological review of analyses on the topic is necessary to glean those approaches and parameter sources that most successfully model real world situations. To inform cycle lengths and possibly group treatments, it was thought prudent to examine actual usage of second line targeted therapies, length of time on them and their per person costs. Thus, this analysis will consist of three linked aims:

1. Systematic review of modeling methodologies for the cost-effectiveness of targeted drugs as second line treatment for rheumatoid arthritis.
2. Determine real world utilization patterns and costs of targeted drugs.
3. Cost-utility analysis of RA treatment options after initial TNFi failure.

The question to be answered is this: What is the most cost-effective treatment for rheumatoid arthritis patients who have failed their first TNFi drug?

METHODS

Human Subjects, Animal Subjects, or Safety Considerations

This study was approved by the University of Texas M.D. Anderson Cancer Center Institutional Review Board (PA17-0789) under expedited review. Waivers of informed consent and authorization were granted as only de-identified and previously published data was used.

The project was also determined as qualifying for exempt status by the Committee for Protection of Human Subjects of University of Texas Health Science Center at Houston (HSC-SPH-18-0164).

JOURNAL ARTICLE 1

Systematic review of economic evaluations of cycling versus swapping in patients with rheumatoid arthritis after failure to tumor necrosis factor inhibitors

Annals of Rheumatologic Disease

ABSTRACT

***Objective**:* To systematically review the modeling approaches and quality of economic analyses comparing cycling tumor necrosis factor-alpha inhibitors (TNFi) to swapping to a therapy with a different mode of action in patients with rheumatoid arthritis whose initial TNFi failed.

***Methods**:* We searched electronic databases, gray literature, and references of included publications until July 2017. Two reviewers independently screened citations. Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Data regarding modeling methodology were extracted.

***Results**:* We included 7 articles comprising 19 comparisons. Three studies scored ≥ 16/24 on the CHEERS checklist. Most models used a lifetime horizon, took a payer perspective, employed a 6-month cycle length, and measured treatment efficacy in terms of the American College of Rheumatology improvement criteria. We noted possible sources of bias in terms of transparency and study sponsorship. In the cost-utility comparisons, the median incremental cost-effectiveness ratio (ICER) was US $70,332/quality-adjusted life-year (QALY) for swapping versus cycling strategies. Rituximab was more effective and less

expensive than TNFi in 7 of 11 comparisons. Abatacept (intravenous) compared to TNFi was less cost-effective than rituximab. Common influential parameters in sensitivity analyses were the rituximab dosing schedule, assumptions regarding disease progression, and estimation of utilities.

***Conclusion**:* Differences in the design, key assumptions, and model structure chosen had a major impact on the individual study conclusions. Despite the existence of multiple reporting standards, there continues to be a need for more uniformity in the methodology reported in economic evaluations of cycling versus swapping after TNFi in patients with RA.

SIGNIFICANCE AND INNOVATION

- First study to review cost-effectiveness analyses comparing cycle versus swap strategies in rheumatoid arthritis patients who have failed their first tumor necrosis alpha inhibitor.
- Reiterates need for standardization and transparency in cost-effectiveness studies.
- Highlights the need of further studies evaluating cost-effectiveness with swapping choices other than rituximab or intravenous abatacept that better reflect current clinical practices.

Therapy with tumor necrosis factor inhibitors (TNFi) has greatly improved the management of patients with rheumatoid arthritis (RA); however, substantial numbers of patients do not experience an adequate response to these drugs, necessitating a change in treatment regimen. The choice of a subsequent therapy is controversial for many reasons, among them doubts about efficacy, concerns about safety, and pervasive resource constraints; adalimumab and etanercept together accounted for over 5% of US pharmaceutical spending in 2013 (1).

Two basic approaches are used after TNFi failure: patients can switch either to another TNFi (cycling strategy) or to a drug with a new mechanism of action (MOA) (swapping strategy). While systematic reviews of randomized controlled trials show that targeted drugs have similar effectiveness and safety profiles (2, 3), evidence from a randomized controlled trial (4) and multiple observational studies (5-13) has supported a swapping strategy. Despite this, physicians tend to cycle rather than swap (10, 14-16), though this trend may be changing (14, 17).

Results from economic evaluations comparing the cycling and swapping strategies have been inconclusive. Cycling appears to be the cheaper strategy (16, 18, 19), but cost-effectiveness analyses show that swapping has an incremental cost-effectiveness ratio (ICER) below willingness-to-pay thresholds and may, in some circumstances, be cost-saving (20, 21).

Our objective was to systematically review the modelling approaches and quality of economic evaluations comparing cycling versus swapping in patients with RA who have failed TNFi therapy.

METHODS

We followed the 27-item checklist of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to report our results (22).

Eligibility criteria

We included: 1) economic evaluations (cost-effectiveness, cost-utility, or cost-benefit analyses); 2) published before July 2017; 3) comparing TNFi (adalimumab, certolizumab, etanercept, golimumab, or infliximab) to non-TNFi biologics (abatacept, anakinra, rituximab, tocilizumab) or tofacitinib (oral small molecule inhibitor); and 4) consisting of patients with RA who had failed a TNFi. We excluded studies: 1) if the comparator group was a disease-modifying anti-rheumatic drug (DMARD); 2) if they were conference abstracts or poster presentations; or 3) if model details were not provided.

Information sources

The search aimed to find published and unpublished studies and was developed with the assistance of a health sciences librarian experienced in developing strategies for systematic reviews. Searches were not limited by year or type of publication but were restricted to articles published in English. The databases searched were MEDLINE (Ovid), EMBASE (Ovid), Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Database of Abstracts of Reviews of Effects, Health Technology Assessments, Web of Science, National Guideline Clearing House, National Institute for Health and Clinical Excellence, Agency for Healthcare Research and Quality, Turning Research into Practice,

Health Economic Evaluations Database, EconLit, National Health System Economic Evaluations Database, and Academy of Managed Care Pharmacy Abstracts. In addition, the reference lists of included articles were hand-searched. DistillerSR software (Evidence Partners) was used to store all citations for duplicate checking and screening.

Search

The initial keywords included "rheumatoid arthritis," the generic and brand names of the 10 drugs of interest, their mechanisms of action, "comparative effectiveness research," "costs," and "cost analysis." The detailed MEDLINE search strategy can be found in Appendix B.

Study selection

Two reviewers (ARK, MLO) performed eligibility assessments independently, blinded to author and journal. Disagreements at all stages were resolved through discussion. If agreement could not be reached, a third reviewer (SBC) made a final decision.

Data collection process

To systematically extract data, we developed a form based on the Guide to Community Preventive Services' standard abstraction document (23) and RA-specific guidelines (24, 25). The form was pilot-tested on 5 randomly selected studies and refined accordingly. Data extraction was performed by one reviewer (ARK) and crosschecked by another (MLO).

Data items

We extracted: i) general information such as title, authors, publication year, country, study sponsor; ii) study characteristics: analytic technique, perspective of the study, funding source, reporting quality; iii) modeling features: participants' characteristics, intervention characteristics, disease states (i.e., health states and pathways), cycle length, time horizon, parameters of effectiveness/safety, and costs (drug and non-drug costs), model outcomes (i.e., quality-adjusted life year (QALY) where one QALY is equivalent to one life year spent in full health- and/or cost per responder; iv) ICERs (i.e., the estimated difference in cost between the competing interventions divided by the difference in QALY's gained); and v) assessment of uncertainty and model validation.

Quality appraisal

The selected studies were appraised for reporting quality using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (26) checklist, which consists of 24 items evaluating 6 aspects of an economic study. Items were assessed as "true," "false," or "not applicable or partly true". Because many items consisted of more than one question, if a sub-item was not reported, the entire item was marked as "partly true". The reporting quality of the studies was assessed as the total number of "true" ratings and expressed as a percentage.

Synthesis of results

Data were analyzed using narrative synthesis. Extracted data were tabulated from the studies. Quantitative meta-estimates were not calculated given the heterogenic nature of

economic evaluations. However, we estimated the median and provide the maximum and minimum values as reference. To facilitate comparability, all ICERs were adjusted to 2017 US dollars according to rules specified by the Community Guide (27): costs per QALY were first converted to US dollars using purchasing power parity rates as published by the World Bank (28) and then revised to 2017 values using the U.S. Department of Labor's medical care consumer price index (MCPI) (base period 1982-1984) (29).

We considered an intervention cost-effective if the incremental cost-effectiveness ratio (ICER) fell below a threshold of $100,000/QALY (30). A threshold of $50,000/QALY has been used historically but, recently, thresholds of $100,000 - $300,000 per QALY gained are being considered more appropriate (30-32). Strategies costing less and at least as effective as the comparator are dominating.

RESULTS

Study selection

After exclusion of duplicates, 5221 citations were screened. The 7 included publications comprised 19 comparisons, as four articles examined more than one treatment strategy. Figure 1 shows the study selection flowchart.

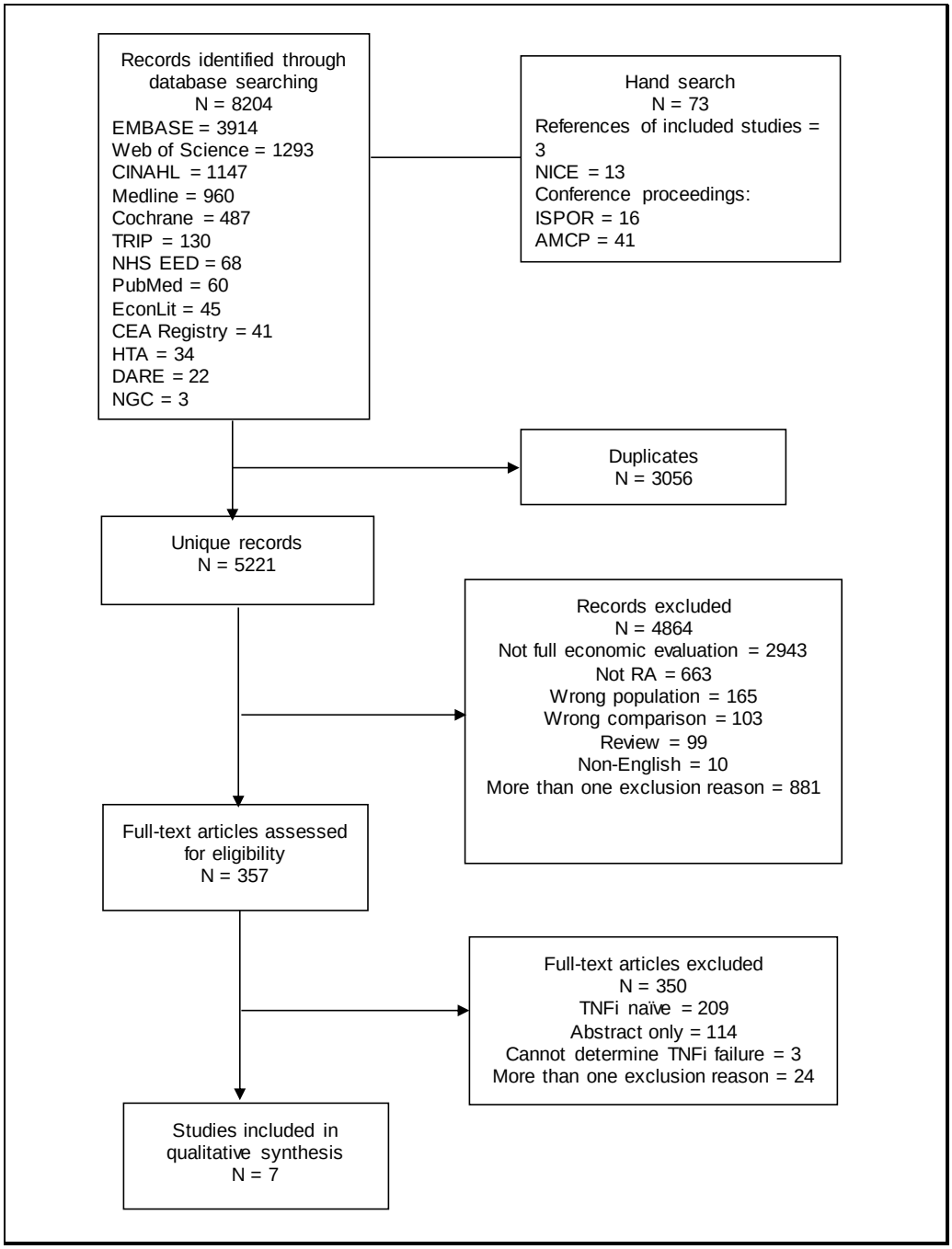

Figure 1.1. Flowchart illustrating the study screening and eligibility evaluation.

This flowchart is modeled after the PRISMA statement (22)

Study characteristics

The 7 included studies represented 4 European countries and the United States. There was one decision tree, three microsimulations, two discrete event simulations and one trial-based study. Four studies were from the perspective of a third-party payer, two took a societal perspective and the 7th did not report perspective. Six models were cost-utility analyses, the last was a cost-effectiveness analysis. Five studies were sponsored by the pharmaceutical industry; all reporting favorable ICERs for their marketed strategy (Table 1).

Table 1.1. Methods and modeling features of the included studies.

Study, year	Country	Model type	Sponsor	Perspective	Horizon	Outcome	Comparisons
Claxton, 2016 (38)	USA	Decision tree	Pfizer	Private payer	1 year	Cost/responder	1
Hallinen, 2010 (39)	Finland	Microsimulation	Roche Oy	Society	Lifetime	QALY	6
Kielhorn, 2008 (37)	UK	Microsimulation	F. Hoffman-La Roche AG	Public payer	Lifetime	QALY	1
Lindgren, 2009 (33)	Sweden	DES	Roche AB	Society	Lifetime	QALY	1
Malottki 2011 (34)	UK	DES	National Institute for Health and Clinical Excellence	Public payer	Not reported	QALY	6
Manders, 2015 (35)	Netherlands	Trial-based	Netherlands Organisation for Health Research and Development	Not reported	1 year	QALY	2
Merkesdal, 2010 (36)	Germany	Microsimulation	Roche Pharma AG, Grenzach- Wyhlen and F. Hoffmann- La Roche Ltd	Public payer	Lifetime	QALY	2

Quality of reporting

While most studies reported their parameters as required by CHEERS (Figure 2), few justified their choices as also recommended by the guideline; for example, most described the study perspective (5 studies), time horizon (6 studies), discount rate (5 studies), health outcomes (all studies) and choice of model (6 studies), but not all gave reason for their choices. No study explained their selection of model. Characterization of uncertainty was another weak point; only 2 studies characterized population heterogeneity. The mean score

(number of "true" answers on the 24-item checklist) was 15 (63.7%), with a range of 11 to 18.

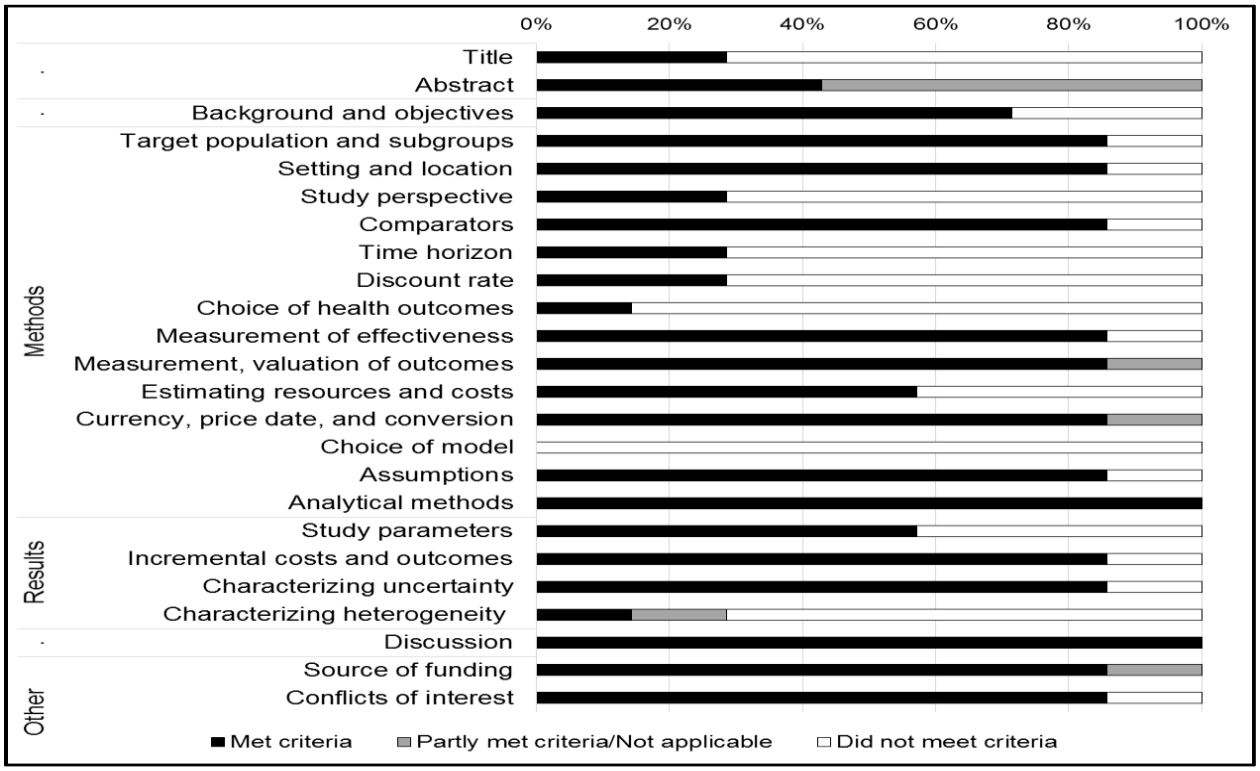

Figure 1.2. Results of CHEERS quality of reporting checklist.

Modeling features

Patient characteristics

Study cohorts were modelled on registries (33, 34), clinical trials (35-37) or epidemiological data (38, 39). Cohorts modelled a population that was predominantly female (median 81%, range, 67-81%), with a median age of 52 years (range, 48-56), disease duration of 10.2 years (range, 6.3-14.1) and baseline Health Assessment Questionnaire Disability Index (HAQ-DI) of 1.88 (range, 1.4-1.9), and weight of 73.8 kg (range, 70.0-77.7).

No study reported all characteristics; 2 studies reported 4 (33, 35), three studies did not report baseline HAQ-DI and one study did not report any patient characteristics at all (38).

Treatment Strategies

Eleven of nineteen comparisons evaluated rituximab versus TNFi, either as a class (33, 35) or individually, with adalimumab being the most common comparator (34, 36, 37, 39). Seven comparisons evaluated abatacept versus TNFi. In one study, tofacitinib was compared to adalimumab.

Health states and pathways

The three microsimulations and two discrete event simulations had at least two health states/events: “on treatment” and “death” (33, 34, 36, 37, 39). Patients on treatment could have varying degrees of response, those not responding moved to the next treatment in sequence or to palliative treatment. One study (33) allowed patients to be off treatment and another (36) had a separate state for palliative treatment. In all cases, costs and utilities were not allocated based on the disease state itself, but on the specific drug, cycle (first vs subsequent) and the associated HAQ-DI score. In all cost-utility analyses the HAQ-DI improved upon new treatment initiation and deteriorated over time, rebounding to its original value upon treatment discontinuation.

One study (35) was not a decision analysis model but was based on a pragmatic randomized controlled trial. In the decision tree study, (38) patients experiencing an ACR20 response would continue treatment for the next 6 months before being reassessed. 75% of those not responding or experiencing an adverse drug related reaction would switch to the next treatment in sequence and the pattern would then be repeated.

Discontinuation was either after a predetermined treatment time (36, 37, 39) or determined based on observational data (33, 34). Only one study explicitly modeled probability of serious adverse events as a reason for discontinuation (38).

Cycle length

Cycle length represents the minimum amount of time an individual will spend in a health state before the possibility of transition to another. The length of the cycle needs to reflect the underlying disease process such that it can represent the frequency of clinical events and interventions. The three microsimulations and one decision tree used a 6-month cycle length. Of these, only one study stated that the cycle length was determined based on the effectiveness data (6-month clinical trials) (37).

Time horizon

Four of the seven included studies used a lifetime horizon and one is presumed to have done so (34). This is consistent with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) best practices (40). One study (35) tracked outcomes over one year, and one study (38) used both one- and two-year frameworks. Shorter frameworks are preferred by the Outcome Measures in Rheumatology initiative (25) which cautioned against extrapolating beyond the duration of the clinical trial, stating that efficacy estimates past 10 years are unlikely to be clinically acceptable.

Effectiveness and safety

ACR criteria were used by four studies to determine treatment efficacy (36-39). One study (38) only considered whether patients achieved at least an ACR20 response or not. One

study (33) used HAQ-DI scores only, and another (33) combined the HAQ-DI with the DAS28 score. One study (35) used the EuroQol 5-dimensional questionnaire (EQ-5D), a standardized instrument for measurement of health-related quality of life (QoL) that can be converted to utilities. In six studies, the effectiveness measures were based on clinical trial data (34-39); however, one used registry data (33) (Appendix C).

Three studies mentioned adverse events: one (33) explicitly excluded them from the model, one (38) incorporated adverse event data from a meta-analysis into the model structure and costed them, and the third (34) reported using them in the sensitivity analysis without providing further detail. Six models (33, 34, 36-39) did consider treatment discontinuations, which are considered particularly important because they can affect the total treatment cost and thereby the overall cost-effectiveness of treatment.

Costs

Cost parameters were unevenly included across studies: in terms of direct medical costs, all studies included drug costs and at least one other component. Two studies each mentioned direct non-medical costs (38, 39) or indirect costs (33, 36). Drug costs were sourced from national price lists while other medical costs and expected resource use were derived from surveys, literature reviews, national fee schedules and guidelines (Appendix C). Given the large disparity in reporting, it was not possible to reconcile amounts for nondrug cost components.

Drug costs. Medication costs were recorded per dose in five studies, and two simply recorded annual (Appendix D). Regarding the latter, studies often differentiated the first and subsequent years/cycles to accommodate loading doses. Drug costs reported in the only study

from the United States were consistently twice the reported by studies from the European countries. Table 2 shows the per (subsequent) 6-month cycle costs of the 5 most commonly reported biologic drugs in the included studies. Rituximab and infliximab were consistently the least expensive drugs, whereas adalimumab and etanercept were the most expensive. One study did not report drug costs (33).

Table 1.2. Distribution of drug costs per 6-month cycle in 2017 US dollars.

	Drug				
Value	**Abatacept IV**	**Adalimumab**	**Etanercept**	**Infliximab**	**Rituximab**
Mean	11,289	15,325	15,140	8,214	8,471
Median	10,050	11,513	10,986	7,335	7,216
Minimum	8,787	8,647	8,649	6,078	4,482
Maximum	16,268	26,260	25,786	12,107	16,471
Standard deviation	3,394	7,472	9,293	2,674	4,183
Number of studies	4	5	3	4	6

*Only includes drugs that were analyzed in at least 3 studies

Non-medication cost components. Costs other than those of targeted drugs were categorized into 22 different components (Table 3) and studies reported 1-10 of them (median: 8). The most commonly reported direct medical costs were laboratory tests and primary care visits (5 of 7 studies), followed by administration, monitoring, and radiology costs (4 studies each). However, in some studies, administration and monitoring were bundled with medication costs, increasing the difficulty of reconciling the study parameter outputs. Direct nonmedical costs, such as patient time costs and training and education costs, were only included in one model each (38, 39). In general, costs were portrayed broadly; few studies noted the cost assigned per item, and fewer still described the derivation of that cost.

Exacerbating the situation was the studies' use of disparate definitions of each of the components. For example, the radiology category might have included only x-rays in one study, but computed tomography scans, magnetic resonance imaging, ultrasonography, and bone densitometry in another study.

Table 1.3. Reported cost components

	Study						
Cost component	**Claxton**	**Hallinen**	**Kielhorn**	**Lindgren[a]**	**Malottki**	**Manders**	**Merkesdal**
Direct medical							
Drugs	✓	✓	✓	✓	✓	✓	✓
Administration	✓	-	✓	-	✓	-	✓
Monitoring	✓	-	✓	-	✓	-	✓
Primary care visits	✓	✓	✓	-	✓	-	✓
Rheumatologist visits	✓	✓	-	-		-	✓
Other specialist visits	-	-	-	-	-	-	-
Allied health	-	✓	-	-	✓	-	-
Phone consultation	-	✓	-	-		-	
Outpatient	✓		-	-	✓	-	✓
Inpatient	-	✓	-	-	✓	-	✓
Home care	-	-	-	-		-	-
Palliative care	-	-	-	-	✓	-	-
Adverse events	✓	-	-	[b]	[c]	-	-
Aids, devices, and home equipment	-	-	-	-	-	-	-
Non-bDMARD prescriptions	✓	-	-	-	-	-	-
Intra-articular injections	-	-	-	-	-	-	-
Joint replacement		-	-	-	✓	-	-
Radiology	✓	✓	-	-	✓	✓	-
Lab tests	✓	✓	✓	-	✓		✓
Direct nonmedical							
Training/education	✓	-	-	-	-	-	-
Patient travel	-	✓	-	-	-	-	-
Patient time	-	-	-	-	-	-	-
Indirect							
Productivity	-	-	-	✓	-	-	✓

Abbreviation: bDMARD, biologic disease-modifying antirheumatic drug
[a]Included "direct and indirect costs" with no further details
[b]Excluded: assumed similar in both arms
[c]Only included in sensitivity analysis

Model outcomes

Quality-adjusted life-years (QALYs) were the model outcome in all cost-utility analyses. They are derived by multiplying the life-years gained from an intervention by the utility of those years. No study reported total life-years gained. Utilities were derived from

the EQ-5D (35) or from regression formulae predicated on HAQ-DI, the most common (36, 37, 39) was Bansback's equation (41). The outcome of the single cost-effectiveness analysis (38) was measured in terms of cost per responder.

ICERs

In the 18 cost-utility analyses, the median ICER was $70,332/QALY for the swapping strategy, with a range of $24,770 to $239,104/QALY. In 7 of the 11 comparisons between rituximab and TNFi, rituximab dominated TNFi, that is, rituximab was both more effective and less expensive than TNFi (Appendix E). The median ICER for the remaining 4 comparisons of rituximab and TNFi was $24,934/QALY. The comparison of intravenous abatacept and TNFi yielded a higher median ICER of $86,334/QALY. The abatacept ICERs fell into 2 distinct groups: one composed of 4 comparisons from two studies (34, 35), with a median ICER of $73,961/QALY (minimum $42,058/QALY, maximum $86,334/QALY), and the other comprising three comparisons from one study (39), with a median ICER of $223,850/QALY (minimum $195,443/QALY, maximum $223,850/QALY). The source of this discrepancy could not be ascertained because the models differed in terms of their type, structure, assumptions, and variables. Table 4 shows the ICERs for the cost-utility analyses comparisons, including the adjustment rates for conversion to 2017 US dollars. In the single cost-effectiveness analysis comparison (38), swapping to tofacitinib dominated cycling to adalimumab in both the one- and two-year-time horizons.

Table 1.4. Incremental cost-effectiveness ratios (ICERs). "Final ICER" is reported in 2017 US dollars.

Study	Swap	Cycle	Original ICER	Currency, year	PPP[a]	MC inflation factor[b]	Final ICER
Hallinen (39)	RTX	IFX	18,179	€, 2008	0.91	364.07	**$26,021**
Hallinen (39)	RTX	ADA	RTX dominant	€, 2008	0.91	364.07	**RTX dominant**
Hallinen (39)	RTX	ETN	RTX dominant	€, 2008	0.91	364.07	**RTX dominant**
Hallinen (39)	ABA	IFX	156,388	€, 2008	0.91	364.07	**$223,850**
Hallinen (39)	ABA	ADA	136,542	€, 2008	0.91	364.07	**$195,443**
Hallinen (39)	ABA	ETN	167,044	€, 2008	0.91	364.07	**$239,104**
Kielhorn (37)	RTX	ADA	11,601	£, 2004	0.69	310.10	**$25,847**
Lindgren (33)	RTX	TNFi	RTX dominant	€, 2008	0.91	364.07	**RTX dominant**
Malottki (34)	RTX	ADA	RTX dominant	£, 2008	0.70	364.07	**RTX dominant**
Malottki (34)	RTX	ETN	RTX dominant	£, 2008	0.70	364.07	**RTX dominant**
Malottki (34)	RTX	IFX	RTX dominant	£, 2008	0.70	364.07	**RTX dominant**
Malottki (34)	ABA	ADA	46,400	£, 2008	0.70	364.07	**$86,334**
Malottki (34)	ABA	ETN	37,800	£, 2008	0.70	364.07	**$70,332**
Malottki (34)	ABA	IFX	41,700	£, 2008	0.70	364.07	**$77,589**
Manders (35)	RTX	TNFi	RTX dominant	€, 2013	0.80	425.13	**RTX dominant**
Manders[c] (35)	ABA	TNFi	29,998	€, 2013	0.80	425.13	**$8351**
Merkesdad[c] (36)	RTX	ADA	15,565	€, 2008	0.82	364.07	**$24,770**
Merkesdal[e] (36)	RTX	ADA	24,517	€, 2008	0.82	364.07	**$39,017**

Assessment of uncertainty

Methodological uncertainty, which pertains to the appropriateness of analytic decisions, was addressed by six (33, 34, 36-39) studies; the most common items (3 of 6 studies) addressed were the HAQ-DI-to-QoL equation, rebound effect, allowing negative

QoL (states worse than death), and discount rate (adjustment for differential timing of events). Structural uncertainty, which pertains to the theory and assumptions underlying the model, was addressed by changing rituximab scheduling (33, 34, 37, 39) and drug dosage (36) assumptions. One study (34) addressed heterogeneity (first-order uncertainty), which accounts for variability among individuals, by running the model separately for different populations. Six models (33, 34, 36-39) included sensitivity analyses to assess parameter (second-order) uncertainty, which focuses on the imprecision of data inputs: six performed one-way sensitivity analyses, including one (38) that also performed a two-way analysis, and half (33, 34, 36, 37) performed probabilistic sensitivity analysis. One study included a 2-dimensional simulation that combined first- and second-order uncertainty (33). The rituximab dosing schedule (repeated treatments being given every 4-9 months) significantly affected results in five of the six studies evaluating the drug. Other influential parameters were assumptions regarding HAQ-DI, such as progression, rebound effects, and the conversion-to-preference weights.

Validation

Internal and external consistency are important in determining model validity (42). Only one study (34) demonstrated the internal validity of the model by verifying its mathematical logic. No studies established the external validity of their models; no model was calibrated against independent data or tested for predictive validity. All model results did appear valid given the data presented (face validity), and five studies (34, 36-39) reported that their results were consistent with previous models (cross-validity).

DISCUSSION

This systematic review included seven studies that made 19 comparisons between TNFi and agents with other mechanisms of action. Adherence to the CHEERS reporting standard among these studies was moderate, with clear, detailed explanation of modeling choices, methodology, and data sources being suboptimal. Despite the substantial uncertainty inherent in assumptions about disease progression under different treatment options, the included publications agreed that swapping to a non-TNFi targeted agent is a cost-effective alternative to cycling to another TNFi at the $100,000/QALY threshold.

This consensus can, at least partly, be attributed to the largely homogenous structure and efficacy parameters of the included models. The efficacy estimates, while expressed differently, were derived from the same set of randomized clinical trials (Appendix F). However, studies did not take into account safety data as most models are based on results from individual trials comparing an experimental drug to a csDMARD and not on meta-analyses and as such, there is a paucity of data comparing safety differences among the different treatments. The validity of the efficacy parameters would be enhanced had it been possible to base them on meta-analyses rather than on single trials.

Drug's relative ranking per study did differ. While this may reflect price differences across time and countries it may also indicate sponsorship bias (43, 44). More problematic are the large discrepancies and lack of transparency in both the reporting and the inclusion of other cost components which further impedes understanding of differences in results. This opacity around cost estimates and the preponderance of studies funded by one

pharmaceutical company leads to concerns regarding bias: in general assessments performed by independent organizations have been found to result in less favorable ICERs than those funded by pharmaceutical companies (45).

The choice of comparator may be another source of bias: 11 of the 19 comparisons evaluated rituximab versus TNFi which is interesting given that, at least in the United States, 70% of patients who swap to an agent with other mechanisms of action switch to abatacept (19). Furthermore, although golimumab and certolizumab pegol have been on the market since 2009, only the latter was analyzed as an alternative to agents with other mechanisms of action (46); however, new non-TNFi drugs, tocilizumab (model excluded because the patients were TNFi-naïve at entry to model (47)) and tofacitinib, have been explicitly considered. A recent analysis reported non-biologic triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) to be cost-effective in comparison to etanercept when used as first line therapy (48). However, no publications have reported on this approach in patients who have already failed biologic therapy.

Whereas previous systematic reviews (21, 34, 49, 50) have looked at treatment options after the failure of the initial TNFi, the current study is the first to specifically compare the cycling and swapping strategies and the only one to comprehensively assess reporting quality and to investigate modeling differences. Our study was, however, limited by the inherent heterogeneity of the economic evaluations and the need to include only those that could be comparable. Furthermore, while we recognize that it is not always possible to present model details in full, we could only compare information explicitly reported in the

papers this may have resulted in more negative quality assessments than the actual models warrant. Also, only one study from US met our eligibility criteria, therefore, the cost per QALY range reported may not entirely reflect US populations-based cost-utility studies.

Future research should determine the treatment sequences used in real-world clinical practice and the length of time patients continue taking each agent. More detailed analysis of the associated nondrug costs would be helpful, as would guidelines regarding the cost components to be included and standardization of efficacy estimate adjustments. Much of the uncertainty in the models could be attributed to a lack of knowledge regarding how commonly used disease activity, disability, and QoL measures change over time, in reaction to new treatment, and with disease progression as well as how these measures should be converted to utilities. Lastly, as noted, adverse events, a major issue of concern, had not been adequately assessed in the majority of these models owing to a lack of evidence on long-term safety. This is yet another fruitful area for investigation.

CONCLUSION

Despite the findings showing that swapping to non-TNFi targeted agents is cost-effective at the $100,000/QALY threshold, our study highlights the need for further studies evaluating cost-effectiveness with swapping choices other than rituximab or intravenous abatacept that better reflect current clinical practices, of longer-term studies on the progression of RA, of RA costs over time and for greater standardization and transparency in the reporting of economic evaluation studies.

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JOURNAL ARTICLE 2

Real-world treatment sequences, effectiveness and costs of tumor necrosis factor alpha inhibitor (TNFi) cycling versus swapping to a disease-modifying anti-rheumatic drug with a new mechanism of action among rheumatoid arthritis patients who have failed their first TNFi

Arthritis Care and Research

ABSTRACT

Objective: Use a large, commercial administrative claims database, Truven Health MarketScan®, to evaluate sequences of therapeutic drugs used by rheumatoid arthritis (RA) patients who failed their initial tumor necrosis factor inhibitor (TNFi) therapy, mean time until therapy discontinuation and the costs associated with TNFi versus non-TNFi drugs.

Methods: Using the Truven Health MarketScan® Research database we analyzed claims of adult RA patients who switched to their second biological or targeted DMARD (disease-modifying antirheumatic drug) between January 2008 and December 2015. We determined the most common treatment sequences and used survival analysis techniques to **estimate time to therapy discontinuation. We compared costs between adherent and non-adherent patients considering drug and other healthcare costs.**

Results: Of the 10,442 RA patients identified to have failed TNFi, 36.4% swapped to a non-TNFi, of which, a majority (66.8%) switched to abatacept. The remaining 63.5% switched to a cycling regimen (second TNFi), a plurality of whom received adalimumab (41.1%). For subsequent lines, non-TNFi was more frequent. Patients who swapped were significantly (p<

0.001) older and sicker than those who cycled. Survival analysis showed longer time to discontinuation for second line non-TNFi versus TNFi (median: 471 versus 370 days, $p < 0.001$) but no difference in subsequent lines.

While non-TNFi drugs were less expensive for adherent patients, cycling was associated with lower costs overall.

Conclusion: Our study reinforces previous work which found that, while patients are more likely to cycle to a second TNFi, those who swap to a non-TNFi, are more likely to persist on second line treatment. However, cycling appears to be the less expensive strategy overall.

MeSH terms: arthritis, rheumatoid/drug therapy; treatment failure; biological products/therapeutic use

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints affecting 0.4-1.3% of the United States population (1). Total annual societal costs of the disease are approximately $39.2 billion (2) and are rising faster than medical inflation (3). Compared to the general population, RA is associated with increased all-cause mortality and greater morbidity. Currently, there is no curative treatment and, as such, therapy to control symptoms is usually required for life.

The discovery of tumor necrosis factor alpha inhibitors (TNFi) and other biological and targeted synthetic therapies brought new hope to RA patients. More people respond to these drugs, and the response is superior to that attained by conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs). However, biologic and targeted therapies are associated with increased side effects and can cost over $20,000 per year (4).

Over the course of their lifetime, most patients are required to switch medication several times due to the side effects of the drug or lack or loss of efficacy in managing symptoms. A systematic review of studies of TNFi discontinuation rates, based on registry and administrative databases, calculated a mean discontinuation rate of 27% (range 23-32%) after one year and increasing to 52% (46-57%) after five years (5).

There are two basic approaches for TNFi failure: cycling (switching to another TNFi: adalimumab, certolizumab, etanercept, infliximab, golimumab) or swapping (to a drug with another mechanism of action: abatacept, anakinra, rituximab, tocilizumab, tofacitinib) but neither strategy conclusively affects the cost-effectiveness of the second-line drug. As new drugs are showing efficacy and being approved (sarilumab and baracitinib were approved in

2017 and 2018 respectively. Filgotinib, upadacitinib, perficitinib, olokizumab are among those in Phase III trials) there is increased controversy regarding the most effective regimen. There is also much concern over the rising price of these drugs: wholesale acquisition costs for etanercept, adalimumab and tofacitinib increased 80.3%, 68.6% and 44.3% respectively between 2013 and 2016 (6). It is increasingly important to address the issue of value and arrive at a consensus regarding the most cost-effective second-line therapeutic option.

Time to discontinuation of treatment, calculated from administrative data sets have become an acceptable proxy for effectiveness in the absence of randomized clinical trials (7, 8). Many studies have calculated survival times and cost of various treatment strategies based on utilization date but they have been limited in terms of length of follow-up (9-12) and sample size (10, 13-15). Only one study was found that investigated all ten drugs approved by the FDA as of 2017 (13).

Furthermore, existing studies have used a limited lead time which makes it difficult to differentiate between second and subsequent line therapies, instead categorizing treatment as first or non-first line (9, 12, 14, 15).

The objectives of this study were to describe sequences of use of treatment strategies, time to drug discontinuation, drug and other healthcare costs for adult patients with RA who have failed initial TNFi therapy.

METHODS

Data source

This retrospective observational cohort study utilized **individual-level, de-identified, fully adjudicated healthcare claims information from employers and health plans** collected from 1998-2016 in t**he Truven Health Marketscan®** Commercial Claims & Encounters **database. The Marketscan claims databases are fully compliant with the health insurance portability and accountability act of 1996 (HIPPS) (16) hence an institutional waiver from IRB approval was granted.**

Study cohort

We used a validated claims-based algorithm (17-20) to identify adult enrollees (age ≥ 18) with RA, using at least two claims, greater than two months apart, with RA diagnosis codes (ICD-9-CM: 714.x; ICD-10- CM: M05.x, M06.x) (Appendix G) who received their first TNFi between January 1, 2008 and December 31, 2015.

All patients were required to have at least one year of continuous enrolment prior to the first claim for a TNFi and at least one year after initiation of the second drug. The index date was the first claim for a TNFi. Because of left censoring, we cannot account for possible biologic use prior to inclusion in the MarketScan database.

Of this initial cohort, we included only those who subsequently switched to a new drug of interest between January 1st 2008 and December 31st 2015 (Appendix H) . This timeframe was chosen to maximize sample size while mitigating the bias caused by not all ten drugs of interest being available on the market (certolizumab, and golimumab were

approved in 2009 while subcutaneous (SC) abatacept was approved in July 2011 and tofacitinib in November 2012).

We excluded patients with overlapping episodes of targeted drugs (defined as more than one drug within the effective period for that drug) as both American and European guidelines explicitly discourage this concomitant dual therapy (21, 22). Furthermore, we excluded ra patients who, at any time, had at least 2 claims, 60 days apart for non-ra indications of biologic drugs (ankylosing spondylitis, chronic lymphocytic leukemia , non-Hodgkin's lymphoma, Crohn's disease, juvenile idiopathic arthritis, multiple sclerosis, polyarteris nodosa, psoriasis, psoriatic arthritis, spondyloarthropathy, systemic lupus erythematosus, ulcerative colitis, Wegener's granulomatosis) as well as those with severe co-morbidities involving immune-suppression such as HIV, organ transplant and malignancies (Appendix I).

Lastly, we deleted claims with a zero or negative allowed amount. If a patient's index claim was deleted, we removed the patient from analysis.

Study measures

The primary study outcome was time to discontinuation for TNFi (cyclers) versus non-TNFi (swappers) after failure of the first TNFi. Secondary outcomes were time to discontinuation of third through sixth treatment lines, the determination of common treatment sequences after tnfi-failure, drug and all-cause healthcare costs associated with each therapy for all versus adherent and non-adherent patients.

Baseline characteristics

We assessed patient age, gender, year of index TNFi, geographic region, plan type and mean follow-up time. We calculated the Deyo-Charlson comorbidity index (23), from claims in the six months prior to index. Rheumatologic diseases were not counted towards the index.

Sequences

We determined the frequency of patients using different drug sequences to establish the most commonly used treatment patterns after TNFi failure.

Treatment persistence

We compared time to discontinuation between TNFi and non-TNFi drugs. This was calculated as the number of days from initiation to drug switching or discontinuation. Switch date was the date of a new biologic minus one day.

A patient was considered to have discontinued treatment if there was greater than 180-day gap in treatment. We defined the discontinuation date as the last claim date plus days' supply. For claims with a procedure code from the Healthcare Common Procedure Coding System (HCPCS), days' supply was imputed as the dosing interval for intravenous (IV) administration as stated in the product insert. For drugs administered subcutaneously (SC) only, the SC dosing interval was used. For claims using a National Drug Code (NDC), the "DAYSUPP" field was used to determine days' supply. In cases where DAYSUPP was zero or one day, we imputed days' supply as the recommended dosing interval. In cases where the dosing interval was variable, the smallest interval was used.

Previous studies (24-36) used gaps of 30-90 days to determine drug discontinuation but this precludes the possibility of patients stopping treatment due to remission (37) or side effects and restarting after a flare or the side effect has resolved. Many studies reported patients restarting TNFi after 140-207 days (38-40). **We chose 180 days based on our preliminary results showing that more than 25% of patients had gaps longer than 90 days.**

Costs

We calculated two categories of costs comparing adherent and non-adherent patients who cycled versus switched after TNFi failure**:** 1) Direct drug-related costs comprised drug acquisition costs for the drugs of interest; 2) other healthcare costs consisted of all other claims. Adherent patients were those with a medication possession ratio (MPR) of over 80%. For oral and subcutaneous drugs MPR was calculated as the total number of days' supply within the six-month period, divided by 183 days. For intravenous drugs, which do not have days' supply variable, we followed Popp et al and defined adherence as receiving at least 80% of the expected doses, based on the dosing schedules for these drugs (see Appendix 5.) (41). Net payments as reported by the carrier were the primary source for calculating the costs.

Statistical Analysis

We stratified the cohort based on mechanism of action of the second targeted drug (cycling versus swapping) and evaluated unadjusted associations with covariates using t-tests and the Wilcoxon rank-sum test (for non-normally distributed variables) for continuous

measures and the Pearson X^2 test for categorical measures. All calculations were based on two-tailed significance level set at 0.05.

Covariates that differed significantly between cyclers and swappers were entered in a Cox Proportional Hazards model as detailed below.

Survival analysis

Differences between cyclers and swappers in time to discontinuation were compared using the non-parametric Kaplan Meier method. When the difference was statistically significant ($p < 0.05$) we ran a Cox Proportional Hazards model to determine to what extent covariates affect time to discontinuation.

Patients were censored if they were continuously treated with the second (or subsequent) drug. Where we were unable to ascertain discontinuation, patients were censored at the end of the study period or disenrollment.

Because rituximab is given every six to nine months, results may be biased in favor of non-TNFi's, hence the models were run both with and without rituximab.

Cost per treated patient per six months

Six-month healthcare costs were calculated for the first and second 180-day post-index period by aggregating payment for individual claims for each of the second line targeted drugs and dividing by the number of patients receiving each drug for the full period. We calculated these costs for all patients as well as subgroups of adherent and non-adherent patients.

All data analysis was conducted using SAS ® Enterprise Guide, Version 7.15. (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

A total of 10,442 patients with a mean follow-up time of almost three years (1,059 days, SD = 583.1) met the study criteria (Figure 1). Of these, 6,626 (63.46%) people cycled to a new TNFi while 3,816 (36.54%) swapped to a drug with a different mechanism of action. Patients who swapped to non-TNFi drugs were significantly older (53.4 years, versus 51.1, $p < 0.001$) and had higher Deyo-Charlson scores (8.44% with two or more comorbidities, versus 4.63%, $p < 0.001$) than those who cycled. Their mean follow-up time was shorter than patients who cycled (1,023.4 days versus 1,079.9, $p < 0.001$). There were also significant differences in start year of first TNFi, region and plan type (Table 1.) but none in terms of gender.

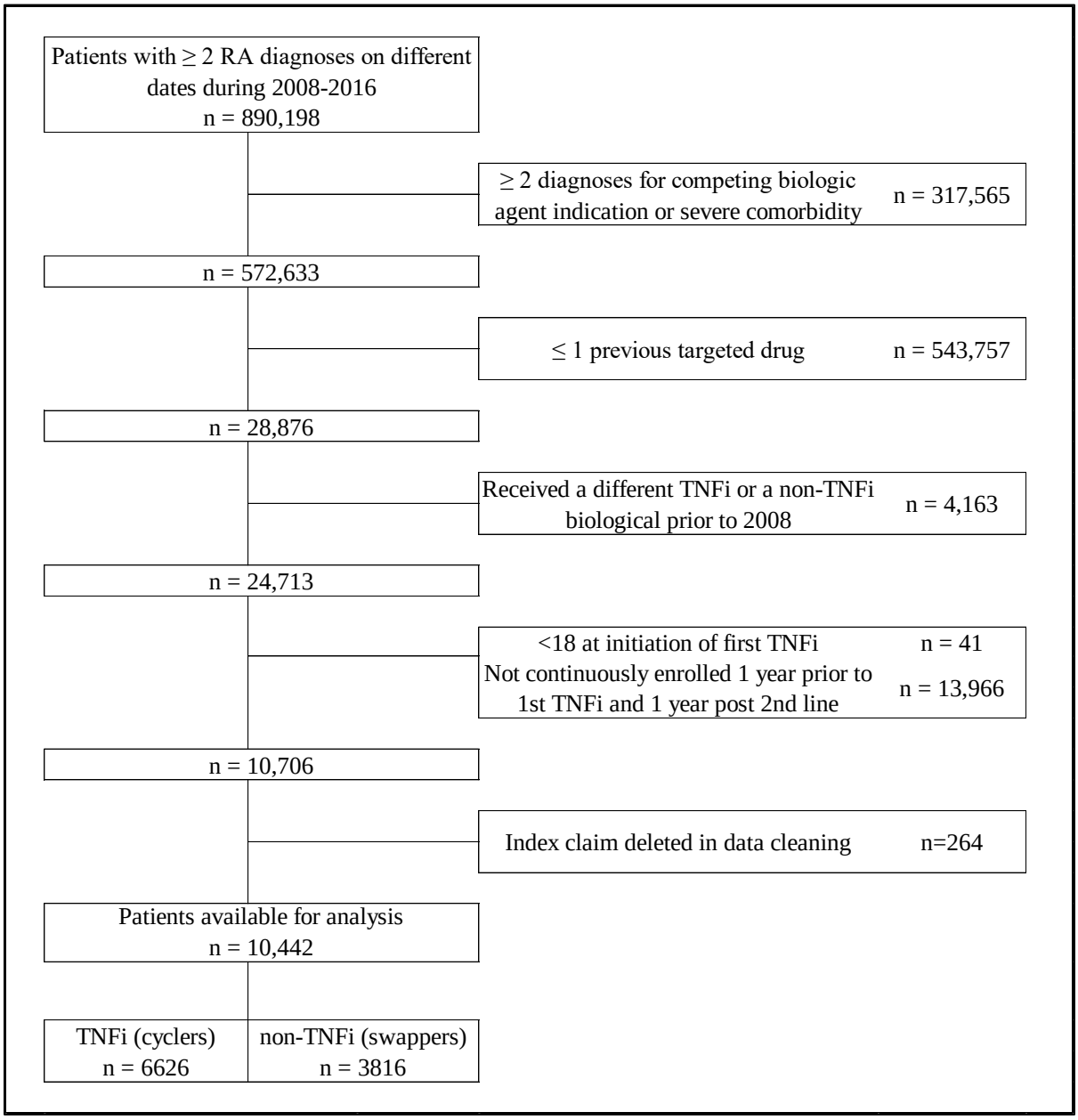

Figure 2.1: Patient selection flowchart

Table 2.1: Demographic characteristics

Variable	**Cycle** n = 6626	**Swap** n = 3816	**P value**
Age: mean (SD)	51.1 (11.59)	53.64 (11.87)	<0.001
% female	79.43	80.69	NS*
Deyo-Charlson score			<0.001
0	80.35%	73.22%	
1	15.02%	18.34%	
2+	4.63%	8.44%	
Region			0.0037
North Central	23.17%	24.74%	
Northeast	15.51%	15.67%	
South	40.51%	40.41%	
West	19.44%	17.16%	
Unknown	1.37%	2.02%	
Plan type			<0.001
Comprehensive	8.10%	12.16%	
Exclusive Provider Organizations	1.09%	1.15%	
Health Maintenance	13.34%	9.38%	
Organization	8.12%	7.36%	
Point-Of-Service	57.29%	58.25%	
Preferred Provider Organization	0.36%	0.31%	
Point-Of-Service – Capitated	5.58%	5.61%	
Consumer-Directed Health Plans	2.60%	2.18%	
High Deductible Health Plans	3.52%	3.59%	
Unknown			
Year of first TNFi			<0.001
2008	26.91%	30.97%	
2009	14.08%	12.08%	
2010	14.20%	12.29%	
2011	11.68%	11.48%	
2012	10.20%	10.06%	
2013	11.24%	12.34%	
2014	8.68%	8.23%	
2015	3.00%	2.54%	
Adherent patients			
First 6 months	53.62%	52.75%	NS*
Second 6 months	33.17%	34.72%	NS*
Follow-up time in days: mean (SD)	1079.85 (590.21)	1023.36 (568.84)	<0.0001

*NS = not significant

Sequences

Etanercept (n=4551, 43.6%) and adalimumab (n=3305, 31.6%) accounted for 75.2% of first-line drugs. Sixty-three percent of patients cycled to a second TNFi (Figure 2), with a plurality switching to adalimumab (41.2%) followed by etanercept (24.3%) (Figure 3). Slightly more than half of cyclers (52.9%) subsequently switched to a third-line drug, the most common being abatacept (30.1%) and etanercept (14.2%).

More than half of swappers (54.2%) switched to abatacept and under half (46.3%) went on to a third-line drug, of which 18.5% switched to tocilizumab and 11.8-14.3% switched to etanercept, tofacitinib or adalimumab. Overall, while TNFi were most often prescribed as second line treatment for RA patients who had failed their initial TNFi, non-TNFi drugs were most common in subsequent lines for both cyclers and swappers (Tables 2 & 3) In all treatment lines approximately 25% of both cyclers and swappers who discontinued treatment did not switch to a new biological or targeted DMARD.

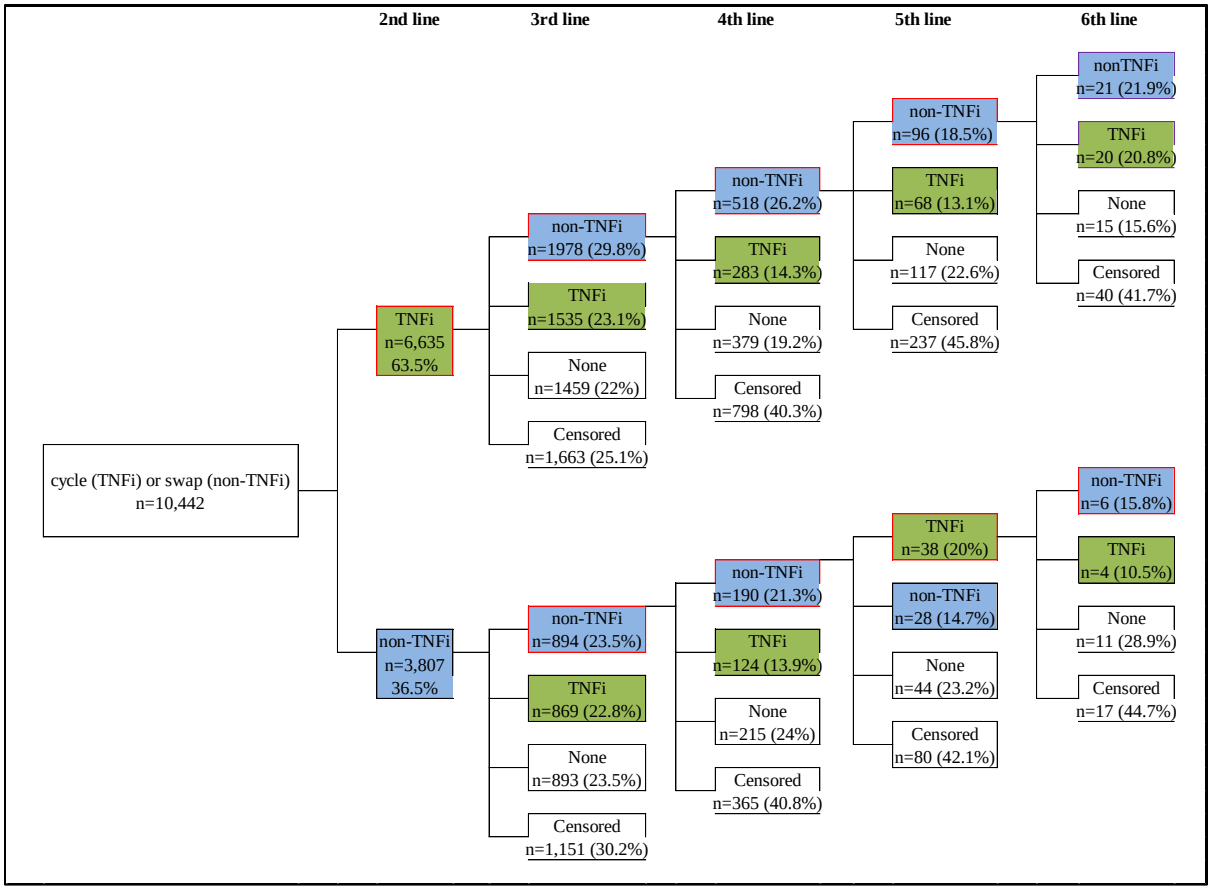

Figure 2.2: Most common sequences by drug class

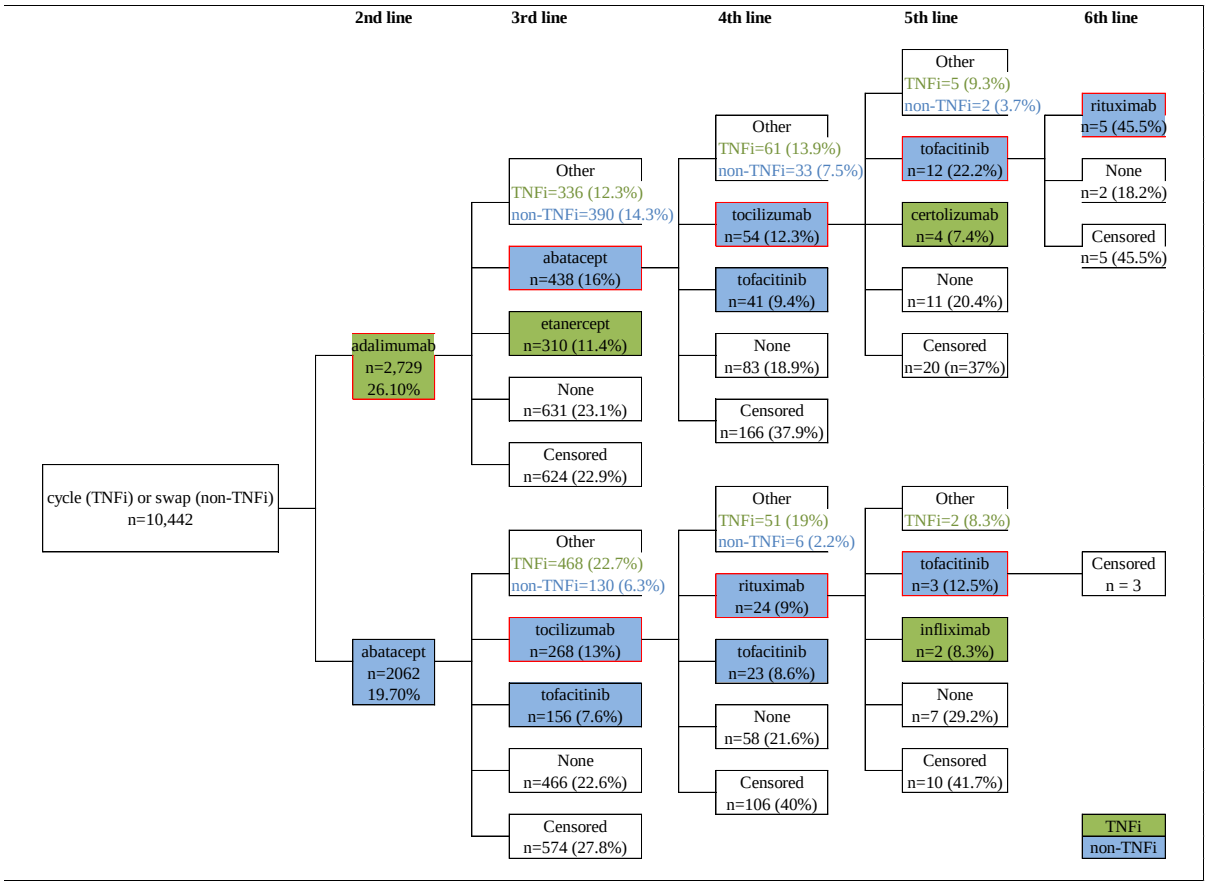

Figure 2.3: Most common sequences by drug

Table 2.2: Second to third line transitions

	Third line TNFi											
	adalimumab		**certolizumab**		**etanercept**		**golimumab**		**infliximab**		**TOTAL**	
Second line	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
TNFi	**303**	**6.5%**	**242**	**5.2%**	**499**	**10.7%**	**251**	**5.4%**	**240**	**5.2%**	**1,535**	**14.7%**
adalimumab	-	-	120	6.3%	310	16.3%	107	5.6%	109	5.7%	**646**	**6.2%**
certolizumab	59	11.9%	-	-	64	12.9%	29	5.8%	18	3.6%	**170**	**1.6%**
etanercept	139	12.0%	71	6.1%	2	0.2%	81	7.0%	66	5.7%	**359**	**3.4%**
golimumab	62	9.8%	40	6.3%	95	15.0%	-	-	37	5.8%	**234**	**2.2%**
infliximab	43	9.2%	11	2.4%	28	6.0%	34	7.3%	10	2.1%	**126***	**1.2%**
non-TNFi	**209**	**24.1%**	**105**	**12.1%**	**253**	**29.1%**	**111**	**12.8%**	**191**	**22.0%**	**869**	**8.3%**
abatacept	110	23.5%	74	15.8%	119	25.4%	66	14.1%	99	21.2%	**468**	**4.5%**
anakinra	2	40.0%	1	20.0%	1	20.0%	1	20.0%	-	-	**5**	**0.0%**
rituximab	28	26.9%	11	10.6%	30	28.8%	10	9.6%	25	24.0%	**104**	**1.0%**
tocilizumab	22	18.0%	9	7.4%	33	27.0%	20	16.4%	38	31.1%	**122**	**1.2%**
tofacitinib	47	27.6%	10	5.9%	70	41.2%	14	8.2%	29	17.1%	**170**	**1.6%**
TOTAL	**512**	**21.3%**	**347**	**14.4%**	**752**	**31.3%**	**362**	**15.1%**	**431**	**17.9%**	**2,404**	**23.0%**

* Ten infliximab patients restarted infliximab after >180 days

	Third line non-TNFi											
	abatacept		**anakinra**		**rituximab**		**tocilizumab**		**tofacitinib**		**TOTAL**	
Second line	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
TNFi	**1,059**	**53.5%**	**5**	**0.3%**	**195**	**9.9%**	**362**	**18.3%**	**357**	**18.0%**	**1,978**	**18.9%**
adalimumab	438	52.9%	3	0.4%	69	8.3%	150	18.1%	168	20.3%	**828**	**7.9%**
certolizumab	121	49.6%	-	-	19	7.8%	53	21.7%	51	20.9%	**244**	**2.3%**
etanercept	259	57.0%	2	0.4%	38	8.4%	70	15.4%	85	18.7%	**454**	**4.3%**
golimumab	114	52.3%	-	-	34	15.6%	39	17.9%	31	14.2%	**218**	**2.1%**
infliximab	127	54.3%	-	-	35	15.0%	50	21.4%	22	9.4%	**234**	**2.2%**
non-TNFi	**154**	**17.2%**	**2**	**0.2%**	**178**	**19.9%**	**326**	**36.5%**	**234**	**26.2%**	**894**	**8.6%**
abatacept	-	-	1	0.2%	129	23.3%	268	48.4%	156	28.2%	**554**	**5.3%**
anakinra	3	75.0%	-	-	1	25.0%	-	-	-	-	**4**	**0.0%**

rituximab	44	43.1 %	-	-	-	-	30	29.4%	28	27.5%	**102**	**1.0%**
tocilizumab	71	43.3 %	1	0.6%	44	26.8 %	-	-	48	29.3%	**164**	**1.6%**
tofacitinib	36	51.4 %	-	-	4	5.7%	28	40.0%	2	2.9%	**70***	**0.7%**
TOTAL	1,213	42.2 %	7	0.2%	373	13.0 %	688	24.0%	591	20.6%	**2872**	**27.5%**

* Two tofacitinib patients restarted tofacitinib after >180 days

	No third line					
	Censored		None		TOTAL	
Second line	**N**	**%**	**N**	**%**	**N**	**%**
TNFi	**1,663**	**53.3%**	**1459**	**46.7%**	**3,122**	**29.9%**
adalimumab	624	49.7%	631	50.3%	**1255**	**12.0%**
certolizumab	165	50.6%	161	49.4%	**326**	**3.1%**
etanercept	434	54.3%	365	45.7%	**799**	**7.7%**
golimumab	229	57.3%	171	42.8%	**400**	**3.8%**
infliximab	211	61.7%	131	38.3%	**342**	**3.3%**
non-TNFi	**1,151**	**56.3%**	**893**	**43.7%**	**2,044**	**19.6%**
abatacept	574	55.2%	466	44.8%	**1,040**	**10.0%**
anakinra	1	14.3%	6	85.7%	**7**	**0.1%**
rituximab	181	54.2%	153	45.8%	**334**	**3.2%**
tocilizumab	220	62.1%	134	37.9%	**354**	**3.4%**
tofacitinib	175	56.6%	134	43.4%	**309**	**3.0%**
TOTAL	**2,814**	**26.9%**	**2,352**	**22.5%**	**5,166**	**49.5%**

Table 2.3: Drug frequency by treatment line

TNFi											
LINE	**adalimumab**		**certolizumab**		**etanercept**		**golimumab**		**infliximab**		**TOTAL**
2	2,729	41.1%	740	11.2%	1,612	24.3%	852	12.8%	702	10.6%	**6,635**
3	512	21.3%	347	14.4%	752	31.3%	362	15.1%	431	17.9%	**2,404**
4	186	23.3%	129	16.1%	180	22.5%	167	20.9%	137	17.1%	**799**
5	45	16.8%	62	23.1%	53	19.8%	61	22.8%	47	17.5%	**268**
6	15	15.3%	22	22.4%	19	19.4%	27	27.6%	15	15.3%	**98**
7	6	15.8%	7	18.4%	7	18.4%	8	21.1%	10	26.3%	**38**
8	-	-	1	16.7%	-	-	3	50.0%	2	33.3%	**6**
9	1	33.3%	1	33.3%	-	-	1	33.3%	-	-	**3**

Non-TNFi											
LINE	**abatacept**		**anakinra**		**rituximab**		**tocilizumab**		**tofacitinib**		**TOTAL**
2	2,062	54.2%	16	0.4%	540	14.2%	640	16.8%	549	14.4%	**3,807**
3	1,213	42.2%	7	0.2%	373	13.0%	688	24.0%	591	20.6%	**2,872**
4	416	30.0%	5	0.4%	212	15.3%	385	27.8%	369	26.6%	**1,387**
5	109	22.3%	5	1.0%	77	15.8%	144	29.5%	153	31.4%	**488**
6	27	14.8%	1	0.5%	46	25.1%	46	25.1%	63	34.4%	**183**
7	6	13.6%	3	6.8%	7	15.9%	10	22.7%	18	40.9%	**44**
8	2	11.1%	-	-	6	33.3%	2	11.1%	8	44.4%	**18**
9	1	50.0%	-	-	-	-	-	-	1	50.0%	**2**

Looking across treatment lines we found a significant ($p < 0.0001$) trend to shorter time to discontinuation for lines two through five (Appendix K). There was no difference for lines five and six.

Table 2.4: Median time to discontinuation (in days) for drugs

	2nd line n = 10,442 **Median (IQR)**	**3rd line** n = 5,276 **Median (IQR)**	**4th line** n = 2,186 **Median (IQR)**	**5th line** n = 756 **Median (IQR)**	**6th line** n = 281 **Median (IQR)**
ALL	**399 (149-760)**	**313 (147-644)**	**252 (112 -539)**	**200 (93-405)**	**194 (112-389)**
p (compared to previous line)		**<0.0001**	**<0.0001**	**<0.0001**	**NS**
TNFi	370 (133-1,175)	504 (166-1,374)	402 (144-1,235)	304 (118-653)	379 (139-1,150)
adalimumab	331 (120-1,007)	439 (151-1,157)	392 (123-1,122)	238 (92-820)	n/a (847-n/a)
certolizumab	339 (128-1,003)	273 (104-813)	237 (83-1,000)	232 (59-507)	210 (139-798)
etanercept	398 (124-1,343)	**722** (223-1,649)	447 (189-1,015)	353 (175-552)	189 (90-n/a)
golimumab	394 (149-1,263)	461 (183-1,027)	419 (189-1,926)	265 (147-942)	308 (168-1,150)
infliximab	542 (214-1,509)	619 (200-2,011)	550 (178 – n/a)	417 (248 – n/a)	553 (130-759)
non-TNFi	471 (180-1,321)	441 (186-1,438)	426 (173-1,217)	339 (156-979)	397 (156-1,013)
abatacept	457 (178-1,316)	393 (175-1,415)	377 (160-885)	244 (153-634)	244 (155-n/a)
anakinra	87 (44-799)	88 (54-162)	84 (84-181)	111 (71-158)	n/a
rituximab	634 (195-1,776)	768 (201-2,306)	1,157 (341-2,051)	1,102 (366-n/a)	830 (683-1,237)
tocilizumab	493 (169-1,384)	466 (171-1,408)	384 (145-1,1254)	287 (137 – n/a)	260 (84-951)
tofacitinib	391 (83-1,049)	431 (125-1,132)	339 (102-1,116)	333 (111-901)	352 (116-985)

Survival analysis

Following Peduzzi et al (42), the minimum sample size for a cox proportional hazards regression is 10k/p where k is the number of predictor variables and p is the proportion of positive cases (failure events) in the population. A further suggestion is that this number be at least 100 (43). We included five predictor models and there were 7,580/10,442, 3,108/5,230, 1,229/2,234, 425/767 and 137/282 failure events for the second through sixth line analyses respectively, hence models could be run for all of them.

The resulting formula for the Cox model for estimating the hazard ratio for discontinuation can be presented as follows:

$h(t) = H_0(t)*\exp(\beta*\text{drug group} + \beta*\text{age} + \beta*\text{age}^2 + \beta*\text{TNF\_start\_year} + \beta*\text{region} + \beta*\text{deyo})$

where $H_0(t)$ represents the baseline hazard, the failure rate when all covariates are set to zero.

The median time to discontinuation for second line TNFi was significantly lower ($p<0.0001$) than that for second line non-TNFi: 370 days (Interquartile range (IQR): 133-1,1175) versus 471 days (IQR: 180-1,321). The Cox model corroborated this. Furthermore, patients with more than two comorbidities were less likely to continue taking their second line drug while older patients were more likely. Thirteen patients did not have verified discontinuation dates and were assumed to be censored.

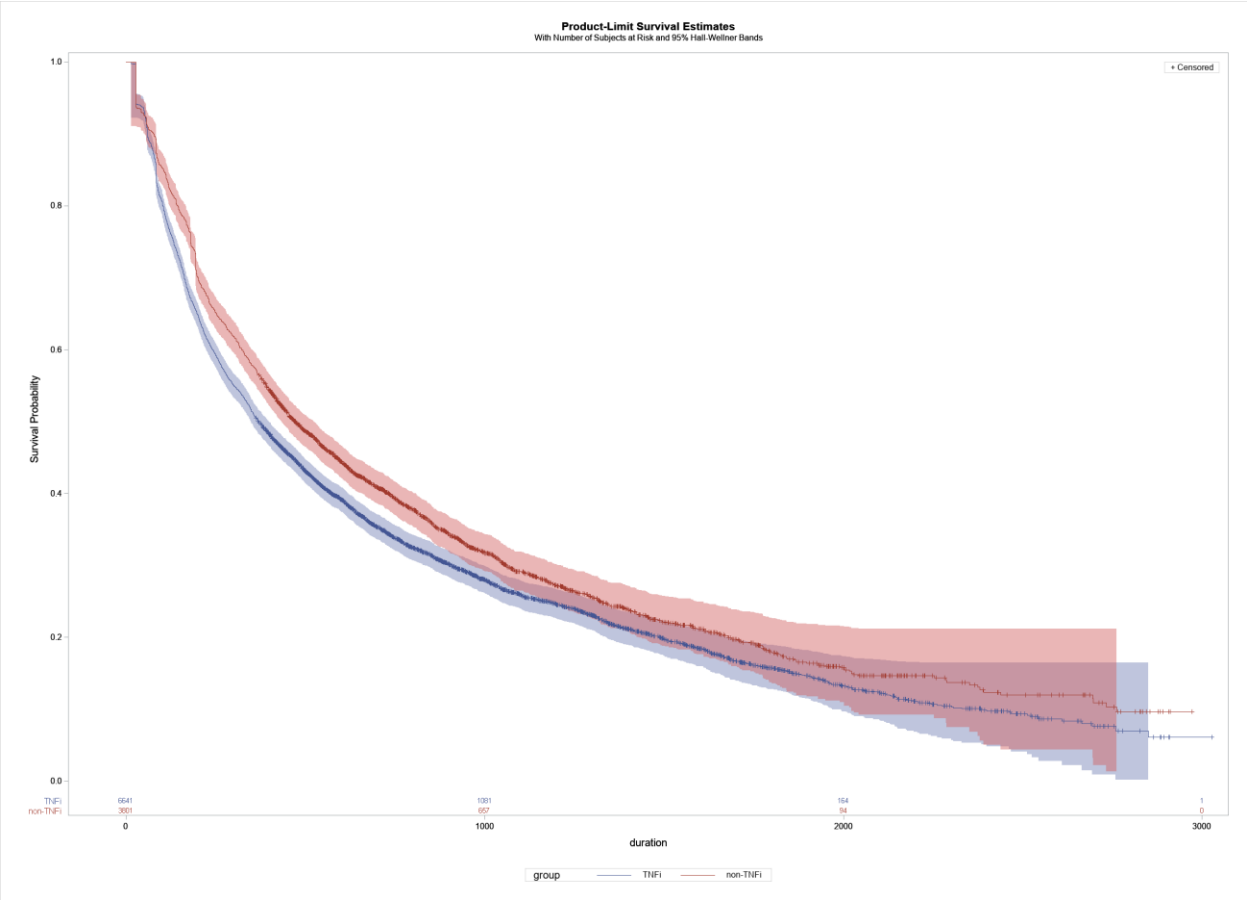

Figure 2.4: Kaplan Meier survival curve for cycling vs swapping

Table 2.5: Cox PH analysis of predictors for second line drug discontinuation

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > Chi Sq	Hazard Ratio	95% Confidence Intervals	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.14017	0.02481	31.9252	**<.0001**	0.869	0.828	0.913
Age	-0.01745	0.00604	8.3505	**0.0039**	.	.	.
Age2	0.0001466	0.0000589	6.1872	**0.0129**	.	.	.
Comorbidity score (ref=0)							
1	0.03253	0.03256	0.9987	**0.3176**	1.033	0.969	1.101
2+	0.15666	0.05009	9.7806	**0.0018**	1.17	1.06	1.29
Region (ref = North West)							
Northeast	-0.03011	0.04026	0.5592	0.4546	0.97	0.897	1.05
South	0.0808	0.03035	7.0903	**0.0078**	1.084	1.022	1.151
Unknown	-0.02215	0.09818	0.0509	0.8215	0.978	0.807	1.186
West	0.07956	0.03661	4.7234	**0.0298**	1.083	1.008	1.163
Year of first TNFi (ref=2008)							
2009	0.08623	0.03945	4.7776	**0.0288**	1.09	1.009	1.178
2010	0.11462	0.03916	8.5686	**0.0034**	1.121	1.039	1.211
2011	0.2769	0.04062	46.4726	**<.0001**	1.319	1.218	1.428
2012	0.23981	0.04308	30.9925	**<.0001**	1.271	1.168	1.383
2013	0.26708	0.04224	39.9732	**<.0001**	1.306	1.202	1.419
2014	0.44033	0.04692	88.066	**<.0001**	1.553	1.417	1.703
2015	0.63067	0.07298	74.6749	**<.0001**	1.879	1.628	2.168
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	-0.09435	0.05192	3.3015	0.0692	0.91	0.822	1.007
Comprehensive	-0.0356	0.04531	0.6173	0.432	0.965	0.883	1.055
Exclusive Provider Organization	-0.27452	0.12185	5.0759	**0.0243**	0.76	0.598	0.965
High Deductible Health Plan	0.10691	0.07414	2.0794	0.1493	1.113	0.962	1.287
Health maintenance Organization	0.02418	0.03696	0.4279	0.513	1.024	0.953	1.101
Point of Service	-0.0196	0.04409	0.1976	0.6566	0.981	0.899	1.069
Point of Service - Capitated	0.16411	0.19708	0.6934	0.405	1.178	0.801	1.734

There was no significant difference in time to discontinuation for third-, fourth- or sixth-line drug classes. Fifth line non-TNFi (n=495) did have a significantly longer time to

discontinuation in the Kaplan Meier model (median 339 days, 95% IQR: 156-979) than TNFi (n=272, median 304 days, 95% IQR: 118-653) but this disappeared when taking covariates into account in the multivariate model.

We conducted a sensitivity analysis by removing the 367 patients who received rituximab. The results changed conclusions for the third line non-parametric analysis, making time to discontinuation significantly longer for patients on third line TNFi. This difference disappeared in the Cox model and seems to be largely accounted for by age and year of first TNFi (See Appendix L. for full results). Conclusions were unchanged for other treatment lines.

For specific second line drugs, the longest-lasting was etanercept among TNFi (mean = 398 days, IQR: 124-1,343) and rituximab among the non-TNFi (mean = 634 days, IQR: 195-1,176). When comparing the most common second line drugs, median time to discontinuation was significantly longer for abatacept (457 days (IQR: 178-1,1316)) compared to adalimumab (331 days (IQR 120-1,007).

Among the most prescribed third line drugs, etanercept (n=752) had a significantly longer median time to discontinuation (722 days (IQR: 223-1,649) than abatacept (n=1213) (393 days (IQR: 175-1,415).

Cost per treated patient

Mean costs across most categories were significantly lower for patients who cycled to a second TNFi. Among patients with a medication possession ratio of at least 80%, mean drug costs were lower for non-TNFi swappers, both for the first six months (not statistically significant) and the second six-month period ($p < 0.001$): $16,128 (SD $6,742) and $15,645 (SD $8.213) for TNFi versus $16,046 (SD $7,129) and $14,454 (SD $6324) for non-TNFi. Other costs tended to be significantly lower for adherent cyclers (for full details see Appendices M & N.) This trend was replicated when looking at the most common second-line-drugs: adalimumab (TNFi) and abatacept (non-TNFi) and could not be accounted for by the higher number of comorbidities among swappers (see Appendix O).

Table 2.6: Mean cost differences between cyclers and swappers

Adherent	Variable	Cycle	Swap	Difference (swap-cycle)	p
ALL	Drug cost: first 6 months	$12,709	$13,053	$344	0.023
	Other costs: first 6 months	$6,138	$8,228	$2,089	<0.001
	Total costs: first 6 months	$18,847	$21,281	$2,433	<0.001
	Drug cost: second 6 months	$7,683	$7,886	$203	NS
	Other costs: second 6 months	$5,100	$7,474	$2,374	<0.001
	Total costs: second 6 months	$12,783	$15,360	$2,577	<0.001
	Annual drug cost	$20,392	$20,939	$547	NS
	Annual other costs	$11,238	$15,702	$4,464	<0.001
	Total annual costs	$31,631	$36,641	$5011	<0.001
YES	Drug cost: first 6 months	$16,128	$16,046	-$82	NS*
	Other costs: first 6 months	$5,594	$8,053	$2,458	<0.001
	Total costs: first 6 months	$21,723	$24,097	$2,376	<0.001
	Drug cost: second 6 months	$15,665	$14,455	-$1,210	<0.001
	Other costs: second 6 months	$5,746	$8,035	$2,289	<0.001
	Total costs: second 6 months	$21,411	$22,490	$1,079	0.047
	Annual drug cost	$31,301	$29,906	-$1,396	0.0035
	Annual other costs	$11,482	$15,435	$3,953	<0.001
	Total annual costs	$42,784	$45,341	$2,557	0.002
NO	Drug cost: first 6 months	$8,756	$9,711	$956	<0.001
	Other costs: first 6 months	$6,767	$8,423	$1,656	0.002
	Total costs: first 6 months	$15,523	$18,134	$2,611	<0.001
	Drug cost: second 6 months	$3,721	$4,393	$671	<0.001
	Other costs: second 6 months	$4,779	$7,176	$2,397	<0.001
	Total costs: second 6 months	$8,501	$11,568	$3,068	<0.001
	Annual drug cost	$14,977	$16,170	$1,193	<0.001
	Annual other costs	$11,117	$15,844	$4,726	<0.001
	Total annual costs	$26,094	$32,01	$5,919	<0.001

* NS = not significant

Table 2.7: Mean cost differences between adalimumab and abatacept

Adherent	Variable	Adalimumab	Abatacept	Difference (swap-cycle)	p
ALL	Drug cost: first 6 months	$12,873	$13,244	$370	0.0208
	Other costs: first 6 months	$5,553	$7,851	$2,299	<0.001
	Drug cost: second 6 months	$7,900	$7,756	-$144	0.0213
	Other costs: second 6 months	$4,543	$7,479	$2,936	<0.001
	Annual drug cost	$20,773	$21,000	$227	NS
	Annual other costs	$10,096	$15,331	$5,235	<0.001
YES	Drug cost: first 6 months	$16,842	$15,513	-$1,329	<0.001
	Other costs: first 6 months	$5,328	$7,593	$2,266	<0.001
	Drug cost: second 6 months	$17,620	$13,669	-$3,950	<0.001
	Other costs: second 6 months	$5,202	$7,654	$2,453	<0.001
	Annual drug cost	$34,159	$28,812	-$5,348	<0.001
	Annual other costs	$10,484	$14,844	$4,361	<0.001
NO	Drug cost: first 6 months	$7,654	$9,776	$2,122	<0.001
	Other costs: first 6 months	$5,849	$8,246	$2,397	<0.001
	Drug cost: second 6 months	$3,600	$3,420	-$180	NS*
	Other costs: second 6 months	$4,252	$7,351	$3,099	<0.001
	Annual drug cost	$14,851	$15,271	$420	NS*
	Annual other costs	$9,925	$15,687	$5,763	<0.001

* NS = not significant

When looking at all ten drugs there were stark differences among adherent and non-adherent patients with tocilizumab and golimumab being the least costly for adherent patients but the costliest for non-adherent patients in the first 6 months. A somewhat more ambiguous pattern was seen when looking at the second six-months and at annual costs, with adalimumab being the costliest for adherent patients (Appendix 9.).

DISCUSSION

This claims-based retrospective analysis assessed treatment sequences, time to discontinuation and costs for 10,442 patients for up to eight years. Our initial results

corroborate those of previous authors who found non-TNFi to be associated with higher persistence despite being prescribed less (9, 11, 13-15, 44). We found one other report of high overall discontinuation rates for biologicals (44). Similarly, while we reported lower drug costs for adherent swappers, like other studies (11, 12, 14, 15), we found that other categories of cost favored TNFi cycling. Despite other studies reporting improved adherence among swappers (9, 14) we found similar adherence between cyclers and swappers.

Patients who began their first TNFi in later calendar years, when there was a greater variety of choices, had shorter times until discontinuation. Prescribing patterns and access issues may explain why patients in the Western and Southern part of the United States were also more likely to discontinue treatment earlier.

The advantages of this study include a larger sample as well as an extended follow-up time and inclusion of all ten targeted DMARDs available on the market at the end of the study period. The most significant strength is the clear identification of second-line versus non-first-line or continuing treatment. Previous publications that made this differentiation were limited by other factors such as reliance on self-report (45) small sample size ($n<201$) (46), follow-up of less than three years (38, 47) or few drugs (47, 48).

As with any data source, MarketScan claims data have limitations. Some have to do with the nature of claims data and others with the nature of the MarketScan sample population. The usefulness of all administrative data sets is constrained in that their purpose is to support reimbursement and not to serve as a research tool; as such there is no

information regarding baseline disease activity, disease severity or response to treatment. The lack of clinical and demographic information precludes propensity score matching which could theoretically compensate for channeling bias whereby specific groups of patients may be more likely to receive (or not receive) certain drugs than others such that results are incorrectly attributed to the drug instead of unmeasured characteristics of the patients. While multivariate modeling does control for some patient characteristics, the nonrandomized allocation of the study groups and baseline heterogeneity introduces bias and confounding. Our study was limited by the number of covariates analyzed compared to similar studies, such as concurrent and pre-index use of csDMARDs, pre-index costs and a greater number of treatment effectiveness criteria.

Accuracy is also a concern in that the diagnosis and procedure codes that do exist may be subject to up-coding, miscoding or may simply be missing if they are not reimbursable. In that vein, Fisher et al (49) report errors in recording days' supply – this supports using a more conservative (shortest possible) cut-off to determine failure.

Regarding MarketScan specifically, because it underrepresents medium and small firms in favor of large employers, the sample is not random, possibly leading to biases and impaired generalizability.

The sample may undercount the newer drugs as claims for newly licensed medications use a non-specific HCPCS code (e.g., J3490 and J3590) until a unique HCPCS code specific to each drug is assigned – this can take up to two years. Because physicians tend to prescribe more familiar drugs first, we believe that this is unlikely to impact results significantly.

Lastly, while time to drug discontinuation is commonly used as a surrogate marker for efficacy, there are other factors that influence retention rates, such as cost (in terms of absolute cost and also patient co-payments), insurance coverage, access to alternative treatments and patient/provider preferences (50). Studies have shown a lowering of the threshold of disease activity before switch over time (50) and a trend of decreasing time to switch (5, 35, 45), specifically, an increasing rate of discontinuations due to inefficacy with no concomitant change in discontinuation rate due to adverse events (51), supporting the contention that the availability of more choices leads to increased switch rates.

Areas for future research include expanding the covariates used in the analysis while preserving the long-follow-up time and analyzing clinical databases which will allow for better matching of patients using more pertinent characteristics such as sero-marker status. Another avenue for study is to determine how, if at all, reasons for switching, affect time to discontinuation of subsequent lines of treatment. Additional data analysis is required first, to corroborate our finding regarding discontinuation of biological and targeted treatment altogether and, secondly, to determine what alternative treatments patients are prescribed. We would also like to further examine reasons for differences in costs between the treatment options.

CONCLUSION

The retrospective claims-based analysis of commercially insured patients adds to the knowledge base by demonstrating how RA patients change treatment over an extended period of time with TNFi being the treatment of choice for second-line treatment while non-

TNFi's are preferred after that. We showed that patients who swap to a drug with a different mechanism of action have longer times to discontinuation compared to those who cycle to a second TNFi. No differences were found for subsequent treatment lines. We report a tendency to lower costs for cycling with the exception of drug costs for adherent patients which were lower for swappers. Our analysis substantiates previous studies that support the use of non-TNFi biological DMARDS for patients who have failed their first TNFi. Patient-specific clinical factors, not available in administrative databases, are needed for more unequivocal evidence.

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JOURNAL ARTICLE 3

Failed initial tumor necrosis inhibitor (TNFi) therapy – what next? Cost-utility analysis of cycling versus swapping to a disease-modifying anti-rheumatic drug with a new mechanism of action among rheumatoid arthritis patients who have failed their first TNFi

Annals of Rheumatologic Disease

ABSTRACT

Objective: To analyze sequences of therapeutic drugs used by rheumatoid arthritis (RA) patients who failed their initial tumor necrosis factor inhibitor (TNFi) therapy in terms of cost-utility, using a microsimulation model following best practice guidelines with parameter inputs based on real-world data.

Methods: We simulated 10,000 RA patients beginning second line biological treatment with adalimumab or abatacept and followed them for up to ten years. In each strategy, patients could either respond or fail to respond to therapy. Those not responding switched to the next drug in a sequence of three. Costs and utilities were assigned based on patients' changing disability status over time. Demographics, treatment sequences, direct medical costs and transition probabilities derived from a cohort of RA patients in the Truven Health MarketScan® Research database were entered into a Markov model using TreeAge Pro 2019.

Results: Switching to a sequence that begins with abatacept versus adalimumab results in an incremental discounted cost of just over $8,000 over ten years and achieves a discounted QALY benefit of 0.14. The incremental cost-effectiveness ratio (ICER) of $61,245/QALY is within current willingness to pay thresholds (WTP). Scenario analysis produced an ICER range of $40,659/QALY to $129,587/QALY. Probabilistic sensitivity analysis results showed that swapping to abatacept after TNFi failure has a 80.6% likelihood of being cost-efficient at a WTP of $100,000/QALY.

Conclusion: Swapping to a treatment sequence beginning with the non-TNFi abatacept was estimated to be a cost-effective strategy for RA patients who have failed their first TNFi therapy.

MeSH terms: cost-utility analysis, arthritis, rheumatoid/drug therapy; treatment failure; biological products/therapeutic use

INTRODUCTION

The promise of rheumatoid arthritis (RA) remission, first seen as a possibility two decades ago when etanercept was approved, has not quite been realized. While many patients do respond and sustain a response to their initial TNFi, many do not (1-4). As of March 2019, there are ten biological and two targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs and tsDMARDs respectively) competing to be a second line agent, all proven efficacious in randomized clinical trials compared to placebo or conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and all expensive. In the absence of, and extreme difficulty in designing, head-to-head randomized controlled trials of complicated treatment sequences, decision analytic models are able to synthesize and extrapolate from the available data. To-date few cost-effectiveness models have considered options after failure of initial TNF-inhibitor. The 30% of patients (1) experiencing this scenario is faced with an expanding range of choices which greatly complicates clinical decision making. There are two basic approaches for TNFi failure: cycling (switching to another TNFi: adalimumab, certolizumab, etanercept, infliximab, golimumab) or swapping (to a drug with another mechanism of action: abatacept, anakinra, baracitinib, sarilumab, rituximab, tocilizumab, tofacitinib) but neither strategy conclusively affects the cost-effectiveness of the second-line drug.

The uncertainty of treatment success, coupled with risk and high expense make these therapies an important target for economic evaluations. These can help fill knowledge gaps regarding population-level effects of the alternative therapies, providing a framework for the comparison of competing interventions thereby assisting decision makers to determine which best serves their needs.

This study aims to provide such a tool by applying best practices to evaluate real-world practice in terms of incremental cost per quality adjusted life year (QALY) of alternative treatments for adult RA patients in the United States who have failed their first TNFi.

METHODS

Philips et al's (5) guidelines for good practice in decision-analytic modeling were followed, with model structure based on best practices as set out in the reference case recommendations made by the U.S. Panels on Cost Effectiveness in Health and Medicine (6, 7). Both of these are, by design, broad and as such, RA-specific methodology will follow Modelling and the Outcome Measures in Rheumatology Clinical Trials (OMERACT) consensus-based reference case for rheumatoid arthritis (8, 9) with input from a systematic review of the rheumatoid arthritis cost-effectiveness literature (10).

Model description and structure

A probabilistic cost-utility microsimulation Markov (state-transition) model was developed in TreeAge Software (TreeAge Software Inc, Williamstown, Mass.). Microsimulation, as opposed to cohort models, allows for the incorporation of heterogeneity and the tracking of events. Markov models are particularly suited to chronic diseases as they allow the mapping of long periods of time while taking into consideration disease progression and varying probabilities. Patients transition between mutually exclusive health states representing clinically and economically distinct events in the disease course. The state

transition diagram (Figure 1) shows the transitions among health states with the arrows on the arc representing the direction of the possible movements. These transitions can occur once per 'Markov cycle'. Figure 2 demonstrates the full Markov model. In keeping with most literature on the subject, cycles were six months long. The first cycle of new treatment is associated with higher cost due to loading doses of the drugs. It is also potentially associated with the highest utility. Under these circumstances we chose not to implement a half-cycle correction which would entail eliminating half of the upfront cost and utility of a new treatment.

Treatment sequences and model input parameters were determined from an analysis of 10,442 patients derived from the Truven Health MarketScan® Commercial Claims & Encounters Databases. The model begins after failure of the patients' first TNFi. Patients pass through sequences of up to three biological drugs after which they shift to palliative treatment.

The analysis was from the perspective of a U.S. private health care payer and, as such only included costs incurred by insurers. The model followed patients from initiation of the second bDMARD for ten years or until death. For the sensitivity analysis we used a lifetime perspective. Theorists prefer a lifetime perspective to reflect the chronic nature of the disease (5) but, for RA specifically, the OMERACT consensus conference cautions against extrapolating beyond available data (8).

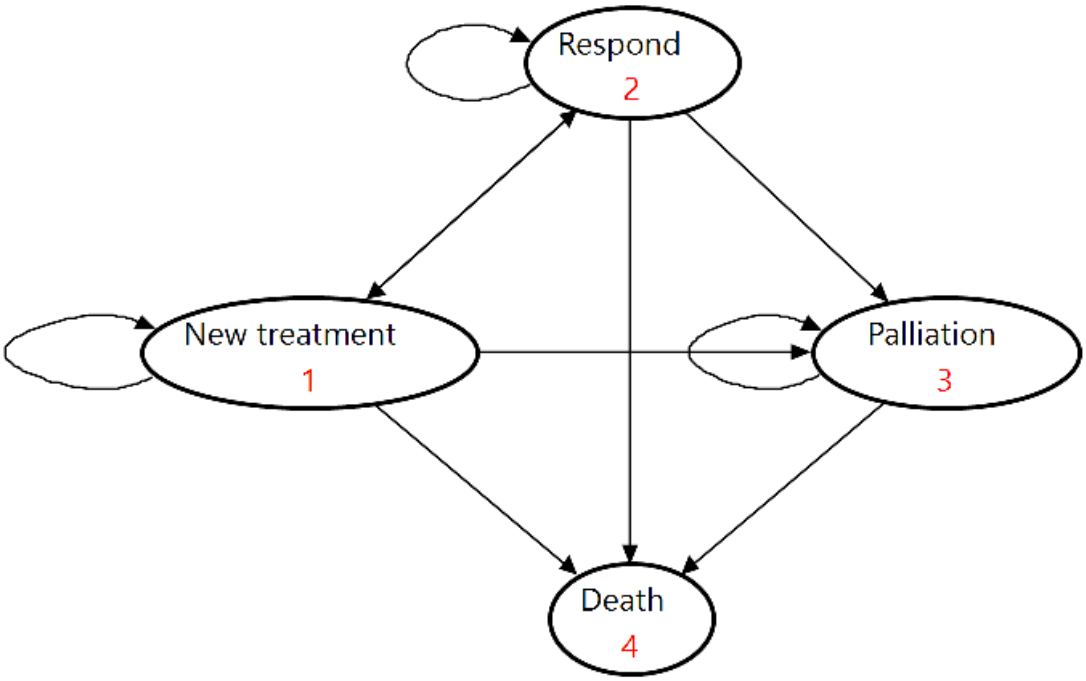

Figure 3.1: State transition diagram

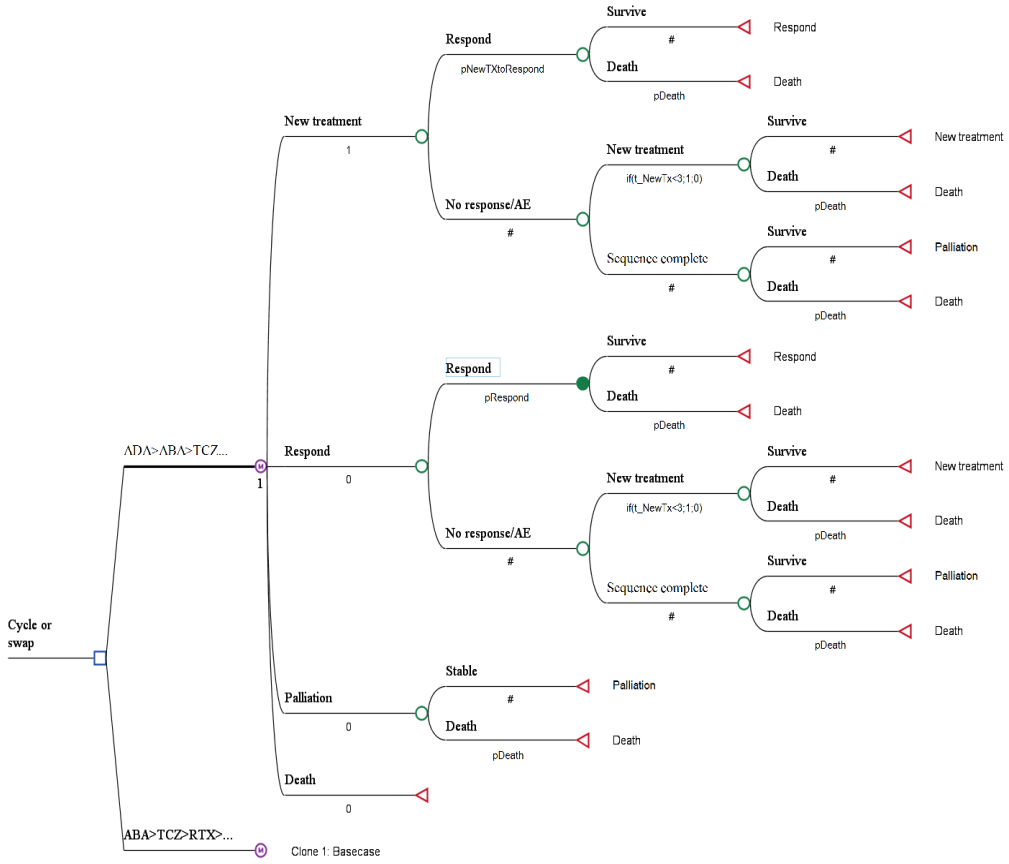

Figure 3.2: Model structure

Population and setting

The cohort consisted of 10,000 individuals, demographically similar to that seen in a large U.S. administrative claims data base in terms of age and gender, who have failed their initial TNFi therapy. Baseline HAQ-DI was derived from a computation of patients' age adjusted comorbidity index (CCIa) which has been shown to correlate with HAQ-DI (11-14). Each CCIa score was mapped to a corresponding HAQ-DI distribution (11) such that patients with the same CCIa could have a range of HAQ-DI scores. Scenario analyses were run

using HAQ values derived from the Birmingham Rheumatoid Arthritis Model (BRAM) (15) and ROC (16) and ATTAIN (17) clinical trials, all of which comprised patients who were refractory to at last one prior TNFi (Table 2).

Table 3.1: Baseline demographic characteristics of the model cohort

Demographical variables	**Value**	**Source**
Females (%)	79.9%	MarketScan
Age (mean ± SD) years	52.03 (11.76)	MarketScan
HAQ-DI score (mean ± SD)	1.46 (0.29)	MarketScan

Treatment sequences

Both the U.S. Panels on Cost Effectiveness in Health and Medicine (6, 7) and the OMERACT consensus-based reference case for rheumatoid arthritis (8, 9) recommend modelling treatment sequences as this is more realistic, with the proviso that these sequences be based on actual practice.

The literature on patterns has mostly concentrated on TNFi's and even then, there is no consensus on the most common second line TNFi: adalimumab (18-21), etanercept (22-24) or infliximab (25). This is likely due to several factors including methodology (self-report versus registry or patient records), country of origin and its treatment guidelines, payment rules and population preferences, as well as availability of alternatives at the time the study was performed. Only one study (18) was found that examined non-TNFi drugs: Baser et al (18) examined data from 3,497 patients starting a second-line agent between 2004-2010 in the Truven Health MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits database and report that abatacept was used 19% of the time, compared to adalimumab, etanercept and infliximab

(31%, 23% and 15% of patients, respectively) and over 70% of the time in those swapping to a non-TNFi. This is a particularly interesting finding given that most studies have concentrated on rituximab as a second line drug (10).

The comparators for this study consist of the most common sequence in each of the cycle and swap categories as ascertained by the analysis of administrative claims data.

- Strategy A: Cycle: adalimumab (ADA) > abatacept (ABA) > tocilizumab (TCZ)
- Strategy B: Swap: abatacept (ABA) > tocilizumab (TCZ) > rituximab (RTX)

We found that while most patients cycle to a second TNFi after initial TNFi failure, non-TNFi drugs predominate in subsequent treatment lines.

Patients who survive the full treatment sequence will continue with palliation. Given the paucity of evidence on the efficacy of csDMARDs following biological or targeted DMARDs, we have not specified what form palliation takes (26).

Health outcomes

Initial and continued treatment response (transition) probabilities were determined from the claims data on a six-monthly basis. They were calculated by dividing the number of patients still on treatment at the end of each six-month treatment by the total number of patients still being followed up in that period. Rates were assumed to be constant after four years.

Responding patients experienced a once-off improvement in disability (HAQ-DI reduction) followed by a disease progression until loss of efficacy (return to baseline HAQ-DI) at which point they switch to the next treatment in sequence.

The HAQ-DI is measured in most RA trials, it is assessed in clinical practice and has been shown to be a close approximation of patients' own evaluation of their health (27), having a fundamental relationship to utility, and a strong correlation with costs and mortality (28, 29)

The term 'utility' refers to cardinal values that represent the strength of an individual's preferences for specific outcomes under conditions of uncertainty. Health utilities specifically, are preferences for distinctive health states or treatments and they allow for the comprehensive measurement of health-related quality of life (30).

QALY's take into consideration both the duration of the effect and its utility. While the validity of QALYs is not uncontroversial it remains the most commonly used measure of health states that facilitates comparisons across diseases.

We converted HAQ-DI to utilities using the formula utilized by the Birmingham Rheumatoid Arthritis Model (BRAM) (15). Sensitivity analyses used 2 other formulas: Bansback (31) because is it the most commonly used and Carreño (32) because it gives much higher values than these and other commonly used formulas (Table 2).

Resource use

Cost parameters and their distributions were gleaned from the analysis of administrative claims data. Net payments as reported by the carrier were the primary source for the calculation. **We calculated two categories of costs**: 1) Direct drug-related costs comprised drug acquisition costs for the drugs of interest; 2) other healthcare costs consisted of all other claims. Each category was further subdivided into initial cycle versus subsequent

cycles to account for loading doses and extra monitoring associated with starting a new treatment. Total costs for each cycle was the sum of drug and other healthcare costs. For palliation, costs were other healthcare costs only. These include costs for csDMARDs and symptomatic treatment.

Costs for the 33 individuals aged over 80 with two or more comorbidities (CCIa=6) were excluded from the base case analysis as they were more than double the next highest CCIa category and likely include end-of-life costs. This impact of this was checked in scenario analysis.

As with utilities, other health related costs were attributed to each individual based on their functional disability score in each cycle. This correlation has been demonstrated in the literature (33, 34).

Given the paucity of studies on productivity losses for the target population, the technical challenges of aggregating outcomes and the debate over methodology and social welfare, this economic evaluation will be from a health-system perspective and as such, will focus on direct medical costs (7, 8, 35).

Table 3.2: Health Assessment Questionnaire Parameters

HAQ to utility formula	
Source	**Conversion to utilities**
Birmingham Rheumatoid Arthritis Model (base case) (15)	utility = 0.804 -0.203*HAQ-DI – 0.045*HAQ-DI^2
Bansback (31)	utility = 0.76 - 0.28*HAQ+0.05*female
Carreño (32)	Utility = 0.9567 - 0.309*HAQ-DI

Baseline HAQ		
Source	**Mean**	**SD**
Truven MarketScan (base case)	1.46	0.29
BRAM (15)	2.0	0.56
ATTAIN trial (17)	1.8	0.6
ROC trial (16)	1.3	0.6

HAQ changes		
Initial response	-0.4	-0.3
Subsequent cycles	0.017	0.01

Table 3.3: Transition probabilities

Strategy A: Cycle: adalimumab (ADA) > abatacept (ABA) > tocilizumab (TCZ)						
β distribution	**Adalimumab (2nd line)**		**Abatacept (3rd line)**		**Tocilizumab (4th line)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Cycle 1	0.6448	0.2500	0.6850	0.1620	0.5876	0.0970
Cycle 2	0.7356	0.1850	0.5858	0.1422	0.6360	0.0727
Cycle 3	0.7133	0.1627	0.6701	0.1039	0.6621	0.0570
Cycle 4	0.7010	0.1391	0.7370	0.0796	0.6979	0.0450
Cycle 5	0.7264	0.1134	0.7344	0.0686	0.7313	0.0363
Cycle 6	0.7468	0.0943	0.6780	0.0622	0.5510	0.0348
Cycle 7	0.7578	0.0803	0.7667	0.0463	0.7778	0.0216
Cycle 8+	0.6992	0.0748	0.6522	0.0457	0.7143	0.0207

Strategy B: Swap: abatacept (ABA) > tocilizumab (TCZ) > rituximab (RTX)						
β distribution	**Abatacept (2nd line)**		**Tocilizumab (3rd line)**		**Rituximab (4th line)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Cycle 1	0.7424	0.1995	0.6459	0.1255	0.9009	0.0435
Cycle 2	0.7573	0.1685	0.6225	0.1023	0.5759	0.0683
Cycle 3	0.7137	0.1546	0.6895	0.0770	0.7364	0.0462
Cycle 4	0.6850	0.1342	0.6335	0.0666	0.7284	0.0400
Cycle 5	0.7535	0.1031	0.6942	0.0507	0.6610	0.0364
Cycle 6	0.7030	0.0949	0.7143	0.0414	0.6410	0.0300
Cycle 7	0.7657	0.0737	0.6000	0.0379	0.6800	0.0233
Cycle 8+	0.7026	0.0696	0.6667	0.0283	0.8235	0.0157

Relative risk of mortality due to RA
Standard US Life tables 2015 (36) * RA risk modifier (29)

Table 3.4: Drug cost parameters

	First cycle drug cost					
γ distribution	**Strategy A: Cycle**			**Strategy B: Swap**		
	Drug	**Mean**	**Std Dev**	**Drug**	**Mean**	**Std Dev**
Second line	ADA	$12,873	$7,277	ABA	$13,244	$7,228
Third line	ABA	$13,244	$7,228	TCZ	$11,984	$7,466

Fourth line	TCZ	$11,984	$7,465	RTX	$16,469	$8,713

Subsequent cycle drug cost						
γ distribution	**Strategy A: Cycle**			**Strategy B: Swap**		
	Drug	**Mean**	**Std Dev**	**Drug**	**Mean**	**Std Dev**
Second line	ADA	$7,900	$9,214	ABA	$7,7556	$7,676
Third line	ABA	$7,756	$7,676	TCZ	$8,365	$8,280
Fourth line	TCZ	$8,365	$8,280	RTX	$8,437	$8,952

Costs and outcomes were discounted at a rate of three percent per annum as recommended by Second Panel on Cost-Effectiveness in Health and Medicine (7).

Model Assumptions

Certain assumptions are required as modelers need to find a balance between accuracy, computability and comprehensibility. In the current analysis, like others (10), we assume that there is an immediate loss of treatment effect after discontinuation. This is based on the expectation that the withdrawal is due to loss of effect or adverse events, both of which imply loss of therapeutic effect. Furthermore, there is no information on differential returns to baseline between the competing agents.

Due to limited long-term data, and evidence demonstrating similar safety profiles between abatacept and adalimumab (37) the costs and disutilities of adverse events have not been explicitly included in the model. There is also little consensus and standardization within clinical trials and observational studies on how, or even which, adverse events should be reported. Our analysis captured them in the calculation of overall healthcare costs and discontinuation probabilities (38).

Analysis

TreeAge's microsimulation sums the utilities and costs of individual patients (trials) taking a random walk through the model's chance nodes. It uses a Monte Carol pseudo-random series to generate a new state configuration from the current one. A key assumption of Markov models is that this is a memory-less system: the new configuration does not depend on any history prior to the current cycle. This is circumvented somewhat by the use of trackers which count how many new treatments patients have been on and how many cycles they have been in the 'Respond' state. Drug costs differ per treatment, and transition probabilities depend on treatment as well as number of cycles. For the first eight cycles in the 'Respond' state, the Markov chain can thus be said to be non-stationary. Subsequently, the transition probabilities are constant and the chain can be considered stationary although the probability of dying increases over time, with increasing patient age.

Two-dimensional simulation was used to account for both first-order i.e. variability among individuals (trials) and second-order uncertainty i.e. parameter uncertainty (sampling),

Pairwise comparisons were made between treatment sequences and the model outcome will be expressed in terms of the incremental cost effectiveness ratio (ICER), i.e. the marginal cost per Quality Adjusted Life Year gained.

Sensitivity Analysis

An essential step in the modelling process is the sensitivity analyses. Conflicting source data, poor internal or external validity and the necessity of extrapolating or making assumptions lead to uncertainty in most economic evaluations. It is thus necessary to

systematically vary the input parameters and probabilities across their possible ranges and calculate the ICERs based thereon. If the conclusion remains unchanged the result can be said to be robust. If the results are not robust, the sensitivity analysis can point to areas where more information is needed, where uncertainty is most crucial and to variables that have greatest bearing on the conclusion

Threshold analysis seeks to identify the critical value of parameter that would need to be achieved in order for an intervention to be deemed cost-effective. Debate exists over the appropriate benchmark for societal willingness to pay (WTP) per quality-adjusted life year (QALY) gained as well as the appropriateness of the measure itself. It is generally acknowledged that the prevalent $50,000/QALY cost-effectiveness threshold criterion, one that has not been revised to allow for inflation and national variation, is not based on well-formulated justifications for a specific dollar value. For the purposes of this analysis, we have thus also used a $100,000/QALY threshold.

Probabilistic Sensitivity Analysis (PSA) assesses the joint uncertainty across all parameters. Costs, transition probabilities and HAQ-DI changes were assigned distributions and the Monte Carlo simulation recalculated expected values for repeatedly sampling parameter values from these distributions. By iterating this process thousands of times distributions of the incremental costs and effects were obtained.

RESULTS

The model comparing two common strategies after initial TNFi failure show that switching to a sequence that begins with abatacept, an anti-T lymphocyte recombinant fusion protein, will cost approximately $224,000 (discounted) over ten years, compared to $216,000 for the sequence that begins with cycling to adalimumab, a tumor necrosis factor inhibitor. The incremental cost of just over $8,000 achieves a discounted QALY benefit of 0.14 over those ten years for an ICER of $61,245/QALY for the basecase (Table 4).

Scenario analysis resulted in an ICER range from $40,659/QALY to $129,587/QALY with a median of $67,483/QALY (Table 5). This is within the realm of current willingness to pay thresholds. These results calibrate nicely with the BRAM model, keeping in mind their higher baseline disability (15). Their comparison of abatacept versus adalimumab resulted in an ICER of £46,4000 (95% credible interval: £23,100-£152,000) which is equivalent to $86,334 ($42,981 - $282,818) (2017 USD).

Table 3.5: Scenario analysis

	ADA>ABA>TCZ		ABA>TCZ>RTX		Incremental	Incremental	
Cohort = 10,000	Costs	QALYs	Costs	QALYs	Costs	QALYs	ICER
Base-case	$215,851	3.22	$224,182	3.36	$8,331	0.14	$61,245/QALY
Lifetime horizon	$356,350	2.71	$367,335	2.98	$10,985	0.27	$40,659/QALY
5-year horizon	$139,588	2.12	$146,492	2.17	$6,904	0.05	$129,587/QALY
Including CCIa6	$217,252	3.13	$225,617	3.25	$8,365	0.12	$71,830/QALY
Bansback HAQ-QALY	$241,844	3.87	$251,394	4.07	$9,550	0.20	$48,215/QALY
Carreño HAQ-QALY	$215,244	4.05	$224,234	4.19	$8,990	0.14	$64,755/QALY
No negative QALY	$216,234	3.23	$224,440	3.36	$8,205	0.13	$64,175/QALY
ATTAIN HAQ	$225,611	2.22	$235,838	2.37	$10,227	0.14	$71,050/QALY
ROC HAQ	$205,158	3.59	$214,692	3.72	$9,534	0.14	$69,186/QALY
BRAM HAQ	$236,208	1.92	$246,504	2.02	$10,296	0.10	$102,076/QALY

Probabilistic sensitivity analysis suggests that the swapping strategy has an 80.6% probability of having an ICER below $100,000 compared with a 37.1% probability at the more conservative $50,000/QALY threshold.

The cost-effectiveness acceptability curve (Figure 2) summarizes some of the uncertainty in the analysis by demonstrating the probability of an alternative being cost-

effective across a range of willingness-to-pay thresholds – given the available data. The abatacept strategy becomes more likely to be cost-effective at just under $60,000/QALY.

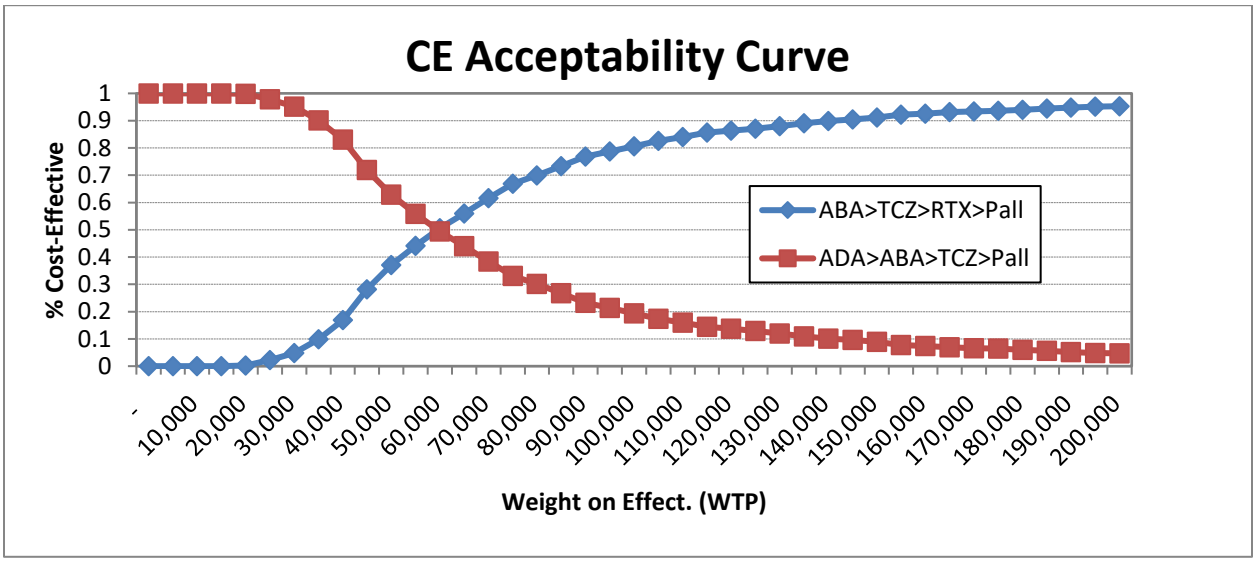

Figure 3.3: Cost-Effectiveness Acceptability Curve

Looking at the incremental cost effectiveness scatterplots, one sees that while the ABA>TCZ>RTX can be cost-effective at the $50,000/QALY threshold (Figure 3a), it is more likely to be so with a higher willingness-to-pay threshold (Figure 3b).

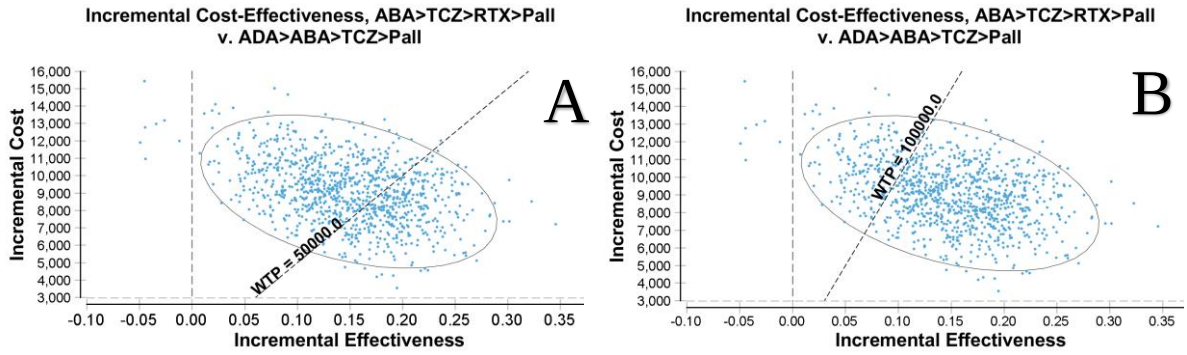

Figure 3.4: ICE Scatterplots

(A: WTP=$50,000/QALY B: WTP = $100,000/QALY)

DISCUSSION

Few studies have compared cycling to swapping, those that have utilized a variety of methodologies and parameters, resulting in a wide range of ICERs. None were based on a US population. In addition, transparency regarding data sources and methodological details is an issue. This leads to concern about biases, particularly since it has been found that assessments performed by independent organizations result in less favorable ICERs than those funded by pharmaceutical companies (39). Publicly funded studies are not yet available for all agents, indeed, for the newer agents, no analysis of their cost-effectiveness as second-line treatment was found at all.

Our baseline mean HAQ-DI was lower than that of other CUAs (10) and this can be explained by their reliance of clinical trial data and, in one case, a British cohort: people enrolling in randomized clinical trials tend to have higher disease activity than those in general practice (40, 41) and biologic drugs are used less frequently in the United Kingdom (41). As the primary outcome is incremental effectiveness, this is unlikely to affect direction of results.

The ICER of the swapping strategy was lower over a longer time period and was higher when baseline HAQ-DI was higher. Both can be explained by the greater probability of continuing treatment in the ABA>TCZ>RTX arm. In the former case, the advantages of

staying on treatment and continued lower HAQ-DI leads to decreased costs over time. However, when HAQ-DI is high, the higher costs associated with this strategy counter this.

Joensuu et al (42) reviewed cost-utility analyses of biologics in RA including four studies comparing rituximab or abatacept to one of more TNFi's. All were European studies. The analyses including rituximab conclude that, compared to TNF's, it is either cost-effective at the €30,000 incremental cost effectiveness ratio (ICER) threshold or is the dominant option (cheaper and more effective). The ICERs for abatacept ranged from €47,663 to over 1.2 million euros.

Sullivan et al (43) conclude from their review of 15 articles that cycling to a second TNFi is less likely to be cost-effective whereas swapping to abatacept or rituximab results in an ICER below willingness to pay thresholds and may even be cost-saving.

Our systematic review also found that swapping to a non-TNFi agent is a cost-effective alternative to cycling to a second TNFi, at the $100,000/QALY threshold (10). The median ICER was $70,332/QALY, compared to this model's $67,483/QALY.

Decision-analysis models are, by definition, simplifications of complex processes and as such cannot capture the full nuance of real-life situations. For example, trials have not had the statistical power necessary to determine differences in treatment-specific mortality and adverse event between arms. Likewise, models are only as good as the data that are available to be incorporated into it. So, while population risk stratification is recommended for increased generalizability and application of the model to sub-groups (e.g. seropositivity), the lack of individual demographic and clinical data hampers this. Similarly, treatment sequences were fixed and do not account for the fact that the choice of the next drug may depend on the

reason for failure of its predecessor: adverse event or primary versus secondary non-response. It is difficult to predict how this would affect results.

The HAQ-DI deterioration rate has been shown to have an impact on study results, and like many others, this study modelled slow, universal HAQ-DI deterioration while on therapy. Lack of data on HAQ-DI progression per second line agent likely impacts the accuracy of the model. Similarly, pain has been shown to be an independent predictor of health-related quality of life and should be incorporated into the HAQ-DI to utility conversion formula (44). This information is not available from administrative databases.

The greatest strength of this model lies in its use of real-world data. Firstly, treatment sequences were chosen in an objective manner with no implicit preference for a particular outcome. This is in contrast to most cost-effectiveness analyses performed. Our systematic review found these to be largely funded by pharmaceutical companies and, either by design or due to publication bias, to favor the sponsor's product. Our analysis allows clinicians to assess actual clinical practice thereby making conclusions particularly pertinent and valid.

An additional advantage of real-world data is the longer-term follow-up which reduces reliance on extrapolation. Randomized clinical trials are limited to one drug and are usually conducted over 6 months. Optional long-term extension studies of up to two years do exist but, overall, there is a paucity of head-to-head studies for second line drugs.

Administrative data also gives access to a more diverse population than that available from strictly controlled clinical trials. Our costs and discontinuation probabilities are derived from community practice. These factors increase the generalizability of our findings to the

larger population. It has also been reported that using data from randomized controlled trials results in lower ICERs than community-based settings (45).

CONCLUSION

To our knowledge, this is the first full cost-utility analysis investigating cycling to a second TNFi versus swapping to a non-TNFi biological drug after failure of first-line TNFi that synthesizes evidence from a United States commercial claims database. Our independent study determined treatment sequences based on an appraisal of real-life prescribing patterns with no preconceived notions of what drugs those sequences should consist of. Similarly, parameter inputs were derived solely from the data. Despite being limited in terms of clinical data our results support and add credence to the existing literature that shows swapping to be a cost-effective strategy for this population.

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APPENDICES

Appendix A: Summary of biological and targeted synthetic therapies

Drug	**Target and structure**	**FDA license**	**Given**	**Dose**	**Loading dose**	**Frequency**
Etanercept	TNFi	Nov 1998	SC	25mg		Fortnightly
(Enbrel)	Soluble fusion protein					
Infliximab+MTX	TNFi	Nov 1999	IV	3mg/kg	w0, w2, w2	q8w
(Remicade)	Chimeric (mouse) MAb					
Anakinra	Anti-IL1	Nov 2001	SC	100mg		Daily
(Kineret)						
Adalimumab	TNFi	Dec 2002	SC	40mg		Fortnightly
(Humira)	Recombinant human MAb					
Abatacept	Anti-T lymphocyte	Dec 2005	IV	500-1000mg	w0 w2 w4	monthly
(Orencia)	Recombinant fusion protein	Jul 2011	SC	125mg		Weekly
Rituximab	Anti-CD20	Mar 2006	IV	100mg		d1 d15 -as needed 6-
(Rituxan)	Chimeric human/mouse MAb	TNFii failure				monthly
Certolizumab	TNFi	Mar 2009	SC	400mg	w0 w2 w4	
(Cimzia)	Pegylated humanized MAb			then 200mg q2w		
				OR 400mg		Monthly
Golimumab	TNFi	Apr 2009	SC	50mg		Monthly
(Simponi)	Human recptor MAb	Jul 2013	IV	2mg/kg	w0 w4	q8w
Tocilizumab	IL-6 receptor	Jan 2010	IV	4mg/kg up to		Monthly
(Actemra)	Humanized MAb	Oct 2013	SC	8mg/kg		Weekly or fortnightly
				162mg		
Tofacitinib	Anti-JAK	Nov 2012	PO	5mg x2/d		Twice daily
		Feb 2016	XR	11mg x1/d		Daily

MAb = monoclonal antibody IL = interleukin JAK =
SC = subcutaneous IV = Intravenous PO = per os XR = extended release

Appendix B: Search strategy. Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid

#	Searches
1	exp ARTHRITIS, RHEUMATOID/
2	((rheumatoid or reumatoid) and arthriti*).ti.
3	((rheumatoid or reumatoid) adj5 arthriti*).mp.
4	ra.ti.
5	(rheumatism* or rheumarthriti*).mp.
6	((rheumatic or reumatic) and (arthriti* or polyarthriti*)).ti.
7	((rheumatic or reumatic) adj5 (arthriti* or polyarthriti*)).mp.
8	(rheumatoid and nodul*).ti.
9	(rheumatoid adj5 nodul*).mp.
10	(rheumatoid and vasculit*).ti.
11	(rheumatoid adj5 vasculit*).mp.
12	((Caplan* or Felty* or Stills* or "Still's" or Sjogren* or Sjoegren* or sicca) and (syndrome* or disease*)).ti.
13	((Caplan* or Felty* or Stills* or "Still's" or Sjogren* or Sjoegren* or sicca) adj5 (syndrome* or disease*)).mp.
14	or/1-13
15	exp TUMOR NECROSIS FACTORS/
16	(tumo?r necrosis factor* adj5 (inhibit* or block* or antagonist* or modulator*)).mp.
17	(TNF* adj5 (inhibit* or block* or antagonist* or modulator*)).mp.
18	(anti-tnf* or antitnf* or TNFi).mp.
19	(anti-tumo?r necrosis factor* or antitumor necrosis factor*).mp.
20	exp RECEPTORS, TUMOR NECROSIS FACTOR/
21	(TNF* adj3 receptor* adj3 (antibod* or anti-bod* or MAb)).mp.
22	(tumo?r necrosis factor* adj3 receptor* adj3 (antibod* or anti-bod* or MAb)).mp.
23	(TNFR* adj3 (antibod* or anti-bod* or MAb)).mp.
24	exp ANTIBODIES, MONOCLONAL/
25	("anti-tumo?r necrosis factor-alpha" adj3 "monoclonal antibod*").mp.
26	ETANERCEPT/
27	(etanercept* or Enbrel* or Embrel* or "TNR 001*" or TNR001*).mp.

28	("tumo?r necrosis factor receptor*" adj3 Fc adj3 "fusion protein*").mp.
29	(TNFR* adj3 Fc adj3 "fusion protein*").mp.
30	(Avent* or CHS-0214* or CHS0214* or Etacept* or Etanar* or GP2015* or GP 2015* or HD203* or HD 203* or LBEC0101* or LBEC 0101* or PRX-106* or PRX106* or Qiangke* or TNFcept* or TuNEX* or Yisaipu*).mp. [etanercept biosimilars]
31	(DWP 422* or DWP422* or SB-4* or SB4* or ENIA-11* or ENIA11* or BX-2922* or BX2922* or Davictrel* or Intacept*).mp. [more biosimilars]
32	ADALIMUMAB/
33	(adalimumab* or Humira* or "D2E7 antibod*").mp.
34	(CTP13* or CT-P13* or SB2* or SB-2* or NI071* or NI-071* or PF06438179* or PF-06438179* or BOW015* or BOW-015*).mp. [biosimilars]
35	INFLIXIMAB/
36	(infliximab* or Remicade* or Revellex* or "MAB cA2" or "monoclonal antibody cA2").mp.
37	(avakine* or IFX or inflectra* or remsima*).mp.
38	(CTP13* or CT-P13* or SB2* or SB-2* or NI071* or NI-071* or PF06438179* or PF-06438179* or BOW015* or BOW-015*).mp. [biosimilars]
39	CERTOLIZUMAB PEGOL/
40	(certolizumab* or Cimzia* or cdp-870* or cdp870*).mp.
41	(PF688* or PF-688*).mp. [biosimilars]
42	(golimumab* or Simponi* or CNTO148 or (CNTO adj "148")).mp.
43	(BOW100* or BOW-100*).mp. [biosimilars]
44	(ozoralizumab* or ATN103* or ATN-103* or PF5230896* or PF-5230896*).mp. [new? anti-TNF]
45	BIOSIMILAR PHARMACEUTICALS/
46	biosimilar*.mp.
47	or/15-46
48	14 and 47 [RA + TNF terms]
49	ECONOMICS/ [Begin NHS EED strategy]
50	exp "COSTS AND COST ANALYSIS"/
51	ECONOMICS, DENTAL/
52	exp "ECONOMICS, HOSPITAL"/
53	ECONOMICS, MEDICAL/
54	ECONOMICS, NURSING/
55	ECONOMICS, PHARMACEUTICAL/

56	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
57	(expenditure$ not energy).ti,ab.
58	(value adj1 money).ti,ab.
59	budget$.ti,ab.
60	or/49-59
61	((energy or oxygen) adj cost).ti,ab.
62	(metabolic adj cost).ti,ab.
63	((energy or oxygen) adj expenditure).ti,ab.
64	or/61-63
65	60 not 64
66	Letter.pt.
67	Editorial.pt.
68	Historical article.pt.
69	Animals/ not humans/
70	or/66-69
71	65 not 70 [End of NHS EED strategy]
72	48 and 71 [RA + TNFi + NHS EED]
73	exp ECONOMICS/ [Begin NHS QI Scotland filter]
74	exp "FEES AND CHARGES"/
75	exp HOSPITALIZATION/
76	CONSUMER SATISFACTION/
77	PATIENT ACCEPTANCE OF HEALTH CARE/
78	DISEASE MANAGEMENT/
79	PHYSICIAN'S PRACTICE PATTERNS/
80	exp "PATIENT CARE PLANNING"/
81	HEALTH CARE RATIONING/
82	QUALITY OF LIFE/
83	VALUE OF LIFE/
84	QUALITY-ADJUSTED LIFE YEARS/
85	"OUTCOME AND PROCESS ASSESSMENT (HEALTH CARE)"/
86	"OUTCOME ASSESSMENT (HEALTH CARE)"/
87	MODELS, ECONOMIC/
88	MARKOV CHAINS/
89	MONTE CARLO METHOD/

90	DECISION TREE/
91	ec.fs.
92	(economic$ or cost? or costing? or costly or costed or price? or pricing? or pharmacoeconomic? or (pharmaco adj economic?) or budget$).tw.
93	(value adj1 money).mp. or (value adj1 monetary).tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
94	(charge? or fee or fees or saving? or preference? or satisfaction or satisfied or ration$ or "quality of life" or qol? or hrqol? or "quality adjusted life year?" or qaly?).tw.
95	(cba or cea or cua or value? or model$ or markov$ or (monte adj carlo) or (decision adj2 (tree? or analys$)) or outcome? or utilit$ or pathway? or protocol?).tw.
96	((clinical or critical or patient) adj path?).tw.
97	((managed adj2 (care or clinical or network)) or (resource? adj1 allocat$)).tw.
98	or/73-97 [End of NHS QI Scotland filter]
99	48 and 98 [RA + TNF + NHS QI Scotland]
100	exp "COSTS AND COST ANALYSIS"/ [econ/cost from current Medline prelim strategy]
101	ECONOMICS, PHARMACEUTICAL/
102	ec.fs.
103	(cost*3 or economic* or pharmacoeconomic* or clinicoeconomic*).ti,kw,sh,jw.
104	(cost*3 adj5 (benefit* or analy* or control* or measur* or averag* or estimat* or evaluat* or annual* or minimiz* or minimis* or minimali* or utilit* or effectiveness or containment)).ab.
105	((econom* or cost*3 or financ* or expenditure* or spend* or spent) adj5 (impact* or model* or evaluat* or analy* or burden)).ab.
106	(ICER* or QALY*).ti,kw.
107	COMPARATIVE EFFECTIVENESS RESEARCH/
108	(comparativ* and (effective* or efficac*)).ti,kw.
109	QUALITY-ADJUSTED LIFE YEARS/
110	or/100-109 [cost/econ terms from current Medline prelim]
111	48 and 110 [RA + TNFi/drug + econ/cost]

Appendix C: Parameter sources

Study	Effectiveness*	Adverse events	Drug costs	Other medical costs	Resource use
Claxton 2016 (38)	RCTs (Keystone et al. 2004; Burmester et al. 2013; Genovese et al. 2005; Cohen et al. 2006)	Meta-analysis (Strand et al. 2015) Drug Package inserts	RED BOOK online (Truven Health Analytics 2015)	U.S. Medicare fee schedule (InGauge Health Care Solutions 2015) The National (Nationwide) Inpatient Sample (Healthcare Cost and Utilization Project (HCUP) 2012)	ACR guidelines (Saag et al. 2008)
Hallinen 2010 (39)	RCTs (Genovese et al. 2008; Maini et al. 1999; Weinblatt et al. 1999; Cohen et al. 2006; Keystone et al. 2004)	n/a	Finnish Medicine Tariff (11/2008)	National health are unit costs in Finland (Hujanen et al. 2008)	National health are unit costs in Finland (Hujanen et al. 2008)
Kielhorn 2008 (37)	RCTs (Maini et al. 1999; Cohen et al. 2006; Keystone et al. 2004)	n/a	British National Formulary	Personal Social Services Research Unit (PSSRU) (Curtis and Netten 2003, 2004) Office for National Statistics (Office for National Statistics 2005) National Health Service (Department of Health & Social Care 2004) Literature review (Barton et al. 2004; Nuijten et al. 2001; Yelin and Wanke 1999)	Norfolk Arthritis Register (Wiles, Cooper, and Symmons 2005)
Lindgren 2009 (33)	Southern Swedish Arthritis Treatment Group Registry, RCT (Cohen et al. 2006)	excluded	Swedish official price list	Swedish Survey (Jacobsson et al. 2007)	Swedish Survey (Jacobsson et al. 2007)
Malottki 2011 (34)	RCTs (Bingham et al. 2009; Bombardieri et al. 2007; Burmester et al. 2007; Genovese et al. 2005; Keystone et al. 2008; Keystone et al. 2009; Westhovens et al. 2006; Bristol-Meyers Squibb 2004; Chen et al. 2006; Cohen et al. 2006; Emery 2005; Hassett et al. 2008; National Audit Office 2009)	RCT's (Bingham et al. 2009; Burmester et al. 2007)	British National Formulary	Systematic review (Chen et al. 2006) Survey (National Audit Office 2009)	Systematic review (Chen et al. 2006) Survey (National Audit Office 2009)
Manders 2015 (35)	Economic evaluation done alongside pragmatic clinical trial: Netherlands Trial Register number NTR1605.				
Merkesdal 2010 (36)	RCTs (Bansback, Brennan, and Ghatnekar 2005; Weinblatt et al. 1999; Edwards et al. 2004;	n/a	German drug retail prices for pharmacists	German recommendations (Deutsche Gesellschaft fur Rheumatologie, DGRh)	German recommendations (Deutsche Gesellschaft

Study	Effectiveness*	Adverse events	Drug costs	Other medical costs	Resource use
	Maini et al. 1999; Genovese et al. 2005; Keystone et al. 2004) Roche internal file				fur Rheumatologie)

*Effectiveness for all included economic evaluations was derived from specific trials of specific medications (in all cases it was biological DMARD vs conventional synthetic DMARD).

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Appendix D: Drug costs

First author	Cost	Unit	Dose	Frequency	6-month cost	Currency	Base year	PPP[a]	USD	MCPI[b]	2017 USD
ABATACEPT IV											
Claxton (38)	849	250 mg vial	Weight dependent		15,290	$	2015	1.00	15,290	446.75	**16,268**
Hallinen (39)	1116	Dose	750 mg	q4w	6696	€	2008	0.91	7341	364.07	**9,584**
Malottki (34)	242	250 mg	750 mg	q4w	4722	£	2008	0.70	6730	364.07	**8,786**
Manders (35)	15,000	Year			7500	€	2013	0.80	9405	425.13	**10,515**
ABATACEPT SC											
Claxton (38)	864	125 mg/mL syringe	125 mg	Weekly	22,466	$	2015	1.00	22,466	446.75	**23,903**
ADALIMUMAB											
Claxton (38)	1898	40 mg/0.8 ml pen	40 mg	q2w	24,681	$	2015	1.00	24,681	446.75	**26,259**
Hallinen (39)	618	Dose	40 mg	q2w	8043	€	2008	0.91	8818	364.07	**11,512**
Kielhorn (37)	358	40 mg	40 mg	q2w	4660	£	2004	0.69	6774	310.10	**10,382**
Malottki (34)	358	Dose		q2w	4648	£	2008	0.70	6623	364.07	**8,648**
Merkesdal (36)	24,914	Year	40 mg	q2w	12,457	€	2008	0.82	15,184	364.07	**19,824**

First author	Cost	Unit	Dose	Frequency	6-month cost	Currency	Base year	PPP[a]	USD	MCPI[b]	2017 USD
CERTOLIZUMAB PEGOL											
Claxton (38)	3344.59	400 mg/2 ml syringe	200 mg	q2w	21,740	$	2015	1.00	21,740	446.75	**23,130**
ETANCERCEPT											
Claxton (38)	932.16	50 mg/ml syringe	50 mg	Weekly	24,236	$	2015	1.00	24,236	446.75	**25,786**
Hallinen (39)	295.19	Dose	50 mg	Weekly	7675	€	2008	0.91	8414	364.07	**10,986**
Malottki (34)	178.78	Dose	50 mg	Weekly	4648	£	2008	0.70	6623	364.07	**8,649**
INFLIXIMAB											
Hallinen (39)	1306.62	Dose	210 mg	q8w	4247	€	2008	0.91	4656	364.07	**6,079**
Kielhorn (37)	419.62	100 mg	3 mg/kg		3431	£	2004	0.69	4987	310.10	**7,644**
Malottki (34)	149.62	Vial			3777	£	2008	0.70	5382	364.07	**7,028**
Merkesdal (36)	15,215.97	Year	3 mg/kg	q8w	7608	€	2008	0.82	9273	364.07	**12,107**
RITUXIMAB											
Claxton (38)	774.07	10 mg/ml vial	2*1000 mg	q6mo	15,481	$	2015	1.00	15,481	446.75	**16,472**
Hallinen (39)	3061.02	Dose	2*1000 mg	q9mo	4592	€	2008	0.91	5034	364.07	**6,573**
Kielhorn (37)	873.15	500 mg	2*1000 mg	q9mo	3493	£	2004	0.69	5077	310.10	**7,782**
Malottki (34)	873.15	500 mg	2*1000 mg	q8.7mo	2409	£	2008	0.70	3433	364.07	**4,482**
Manders (35)	9487.20	Year	2*1000 mg	q6mo	4744	€	2013	0.80	5948	425.13	**6,651**
Merkesdal (36)	11,146.83	Year	2*1000 mg	q9mo	5573	€	2008	0.82	6794	364.07	**8,869**
TOCILIZUMAB IV											
Claxton (38)	819.48	80 mg/ml vial	400ml	once	4097	$	2015	1.00	4097	446.75	**4,359**
TOCILIZUMAB SC											

First author	Cost	Unit	Dose	Frequency	6-month cost	Currency	Base year	PPP[a]	USD	MCPI[b]	2017 USD
Claxton (38)	819.48	80 mg/ml vial		Weekly	21,306	$	2015	1.00	21,306	446.75	**22,669**
TOFACITINIB											
Claxton (38)	52.82	5 mg tablet	5 mg	*2/d	19,279	$	2015	1.00	19,279	446.75	**20,512**
TNFi											
Manders (35)	13,205.00	Year			6603	€	2013	0.80	8280	425.13	**9,258**
GOLD SALTS											
Hallinen (39)	5.06	Dose	50 mg	q4w	30	€	2008	0.91	33	364.07	**43**
Kielhorn (37)	2.94	10 mg	25-50 mg	q2-3w	96	£	2004	0.69	139	310.10	**214**
Malottki (34)	11.23	Dose	50 mg		67	£	2008	0.70	96	364.07	**125**
Merkesdal (36)	327.22	Year			163.61	€	2008	0.82	199	364.07	**260**
AZATHIOPRINE											
Malottki (34)	0.40	Day	150 mg	Daily	74	£	2008	0.70	105	364.07	**138**
CYCLOSPORINE											
Hallinen (39)	9.54	Dose	210 mg	Daily	1741	€	2008	0.91	1909	364.07	**2,492**
Kielhorn (37)	50.00	100 mg	3.25 mg/kg	Daily	768	£	2004	0.69	1116	310.10	**1,711**
Malottki (34)	5.37	Day	225 mg	Daily	980	£	2008	0.70	1397	364.07	**1,823**
Merkesdal (36)	5917.22	Year			2959	€	2008	0.82	3606	364.07	**4,709**
Leflunomide											
Kielhorn (37)	51.13	20 mg	15.2 g	Daily	247	£	2004	0.69	359	310.10	**550**
Malottki (34)	1.70	Day	20 mg	Daily	310	£	2008	0.70	442	364.07	**577**
Methotrexate											
Hallinen (39)	1.32	Dose	15 mg	Weekly	34	€	2008	0.91	38	364.07	**49**

First author	Cost	Unit	Dose	Frequency	6-month cost	Currency	Base year	PPP[a]	USD	MCPI[b]	2017 USD
Kielhorn (37)	3.27	2.5 mg	7.5-20 mg	Weekly	18	£	2004	0.69	27	310.10	**40**
Malottki (34)	0.12	Tablet	15 mg	Weekly	18	£	2008	0.70	26	364.07	**33**
Merkesdal (36)	155.74	Year			78	€	2008	0.82	95	364.07	**124**
Palliative											
Malottki (34)	284.00	6 months			284	£	2008	0.70	405	364.07	**528**

[a] Purchasing power parity, data from World Bank

[b] Medical Consumer Price Index, data from US Bureau of Labor Statistics

Appendix E: Point estimates of the cost-utility comparisons

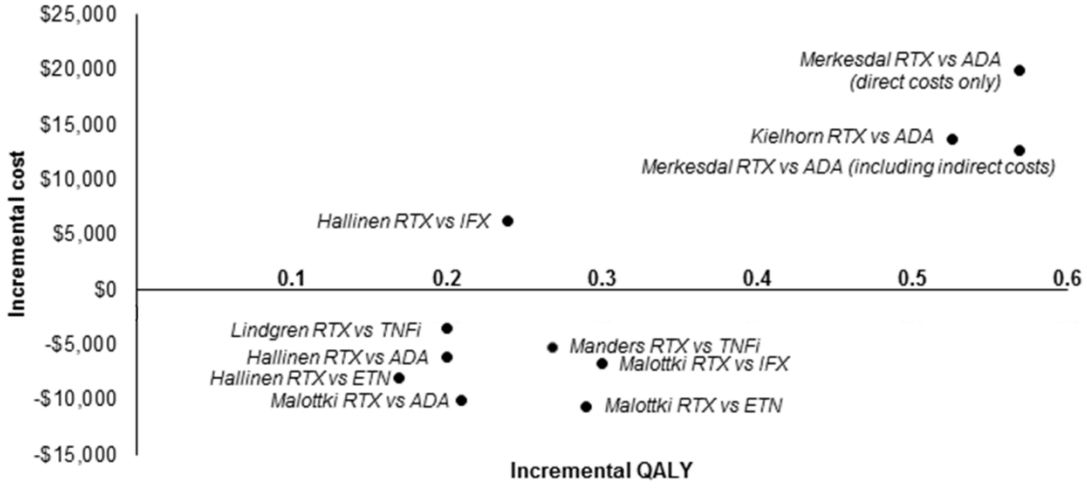

Figure 4a represents the point estimates of the cost-utility comparisons of rituximab (RTX) – a swapping strategy. Health outcomes (incremental quality-adjusted life year (QALY)) are plotted on the x axis and the incremental costs on the y axis. The studies were rituximab generated more health gains reported higher costs. Rituximab was cost-saving in seven of the reported estimates. ADA, adalimumab; ETN, etanercept; IFX, infliximab; TNFi, RTX, rituximab; Tumor Necrosis Factor alpha inhibitor.

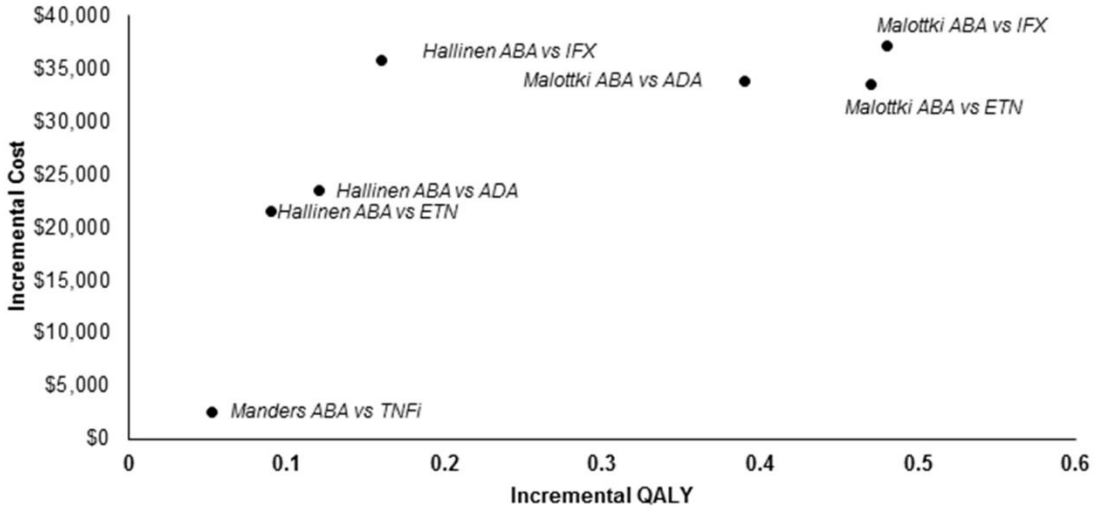

Figure 4b represents the point estimates of the cost-utility comparisons of abatacept (ABA) – a swapping strategy. Health outcomes (incremental quality-adjusted life year (QALY)) are plotted on the x axis and the incremental costs on the y axis. The studies were intravenous abatacept generated more health gains reported higher costs. ABA, abatacept; ADA, adalimumab; ETN, etanercept; IFX, infliximab; TNFi, Tumor Necrosis Factor alpha inhibitor.

Appendix F: Efficacy and utility parameters

Author(s)	Claxton, 2016 (38)	Hallinen, 2010 (39)	Kielhorn, 2008 (37)	Lindgren, 2009 (33)	Malottki, 2011 (34)	Manders, 2015 (35)	Merkesdal, 2010 (36)
Health Assessment Questionnaire (HAQ)							
HAQ progression: bDMARD	n/a	0.017/cycle	0.017/cycle	Linear regression using:starting HAQ, months on treatment, treatment line and disease duration	response maintained	Not reported	0.017/cycle
HAQ progression: cDMARD		n/a	n/a	n/a	0.045/year	n/a	n/a
HAQ progression: palliation		0.065/cycle	0.065/cycle	n/a	0.06/year	n/a	0.065/cycle
HAQ progression: off treatment		n/a	n/a	0.03/year	n/a	n/a	n/a
HAQ after treatment end		return to initial HAQ score		return to initial HAQ score	return to initial HAQ score		n/a
HAQ-QoL conversion		0.76 - 0.28*HAQ+ 0.05*Female	0.76 - 0.28*HAQ+ 0.05*Female	-0.252*HAQ - 0.107*disease activity - 0.05*male + 0.915	a-b1*HAQ-b2*HAQ^2	n/a	0.76-0.28*HAQ +0.05*Female
Health Assessment Questionnaire (HAQ) change associated with ACR							
ACR0-20	n/a	0.1	0.1	n/a	n/a	n/a	0.1
ACR20-50		0.45	0.45				0.45
ACR50-70		0.85	0.85				0.85
ACR70-100		1.11	1.11				1.1
Efficacy							
ADA	Keystone, 2004	Keystone, 2004	Keystone, 2004	Comparator was TNFi in general. No efficacy information reported	n/a	Manders, 2015	Keystone, 2004
	% achieving ACR20/50/70 (degraded)	adjusted ACR response rates (transition probabilities	adjusted ACR response rates			TNFi in general Good/mod EULAR response	adjusted ACR response rates
	48.2/21.2/6.8	0.21/0.16/0.18	0.598/0.369/0.196			0.34/0.72	0.21/0.16/0.18
ABA+MTX	Genovese et al 2005	Genovese et al 2005	n/a	n/a	n/a	Manders, 2015	n/a
	% achieving ACR20/50/70	adjusted ACR response rates (transition probabilities				Good/mod EULAR response	
	50/20/10	0.32/0.11/0.11				0.21/0.68	
ETN	n/a	Weinbaltt et al, 1999	n/a	n/a	n/a	n/a	
		adjusted ACR response rates (transition probabilities					
		0.29/0.22/0.14					
IFX	n/a	Maini, 1999	Maini, 1999	n/a	n/a	n/a	Maini, 1999

Author(s)	**Claxton, 2016** (38)	**Hallinen, 2010** (39)	**Kielhorn, 2008** (37)	**Lindgren, 2009** (33)	**Malottki, 2011** (34)	**Manders, 2015** (35)	**Merkesdal, 2010** (36)
		adjusted ACR response rates (transition probabilities)	adjusted ACR response rates				adjusted ACR response rates
		0.24/0.2/0.08	0.59/0.319/0.094				0.24/0.2/0.08
	Cohen, 2006	Cohen, 2006	Cohen, 2006	Cohen, 2006	n/a	Manders, 2015	Cohen, 2006
	% achieving ACR20/50/70	adjusted ACR response rates (transition probabilities)	adjusted ACR response rates	% achieving ACR20/50/70		Good/mod EULAR response	adjusted ACR response rates
RTX+MTX	51/27/12	0.27/0.17/0.13	0.631/0.334/0148	51/27/12		0.39/0.71	0.27/0.17/0.13
	Burmester et al 2013	n/a	n/a	n/a	n/a	n/a	n/a
	% achieving ACR20/50/70						
TOF	51/37/16						
Adjustment		Ref placebo OR/Trial placebo OR *Trial treatment OR	Ref placebo OR/Trial placebo OR *Trial treatment OR	n/a	n/a		(adjusted Trial Treatment = adjusted OR/(1 + adjusted OR) (adjusted OR = (OR\Average placebo rate/OR\Trial Placebo) +OR\Trial Treatment).
Time on treatment	Probabilistic	Predefined time period	Predefined time period	Probabilistic	Probabilistic		Predefined time period
RTX retreatment interval	6 months	9 months	9 months	6 months	8.7 months	6 months	9 months
Discount rate, effectiveness	n/a	0.03	0.035	0.03	0.035		0.035
Discount rate, cost	n/a	0.03	0.035	0.03	0.035		0.035

ACR, American College of Rheumatology; ADA, adalimumab; ABA, abatacept; bDMARD, biologic Disease Modifying Antirheumatic Drug; cDMARD, conventional Disease Modifying Antirheumatic Drug; ETN, etanercept; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; IFX, infliximab; MTX, methotrexate; n/a, not applicable; OR, odds ratio; RTX, rituximab; TNFi, Tumor necrosis factor alpha inhibitor; TOF, tofacitinib.

Appendix G – RA ICD-10 codes

ICD-10 code	Description
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement

ICD-10 code	Description
M05.721	Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement
M05.722	Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement
M05.729	Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems involvement
M05.731	Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement
M05.732	Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement
M05.739	Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems involvement
M05.741	Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement
M05.742	Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement
M05.749	Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems involvement
M05.751	Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement
M05.752	Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement
M05.759	Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement
M05.761	Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement
M05.762	Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement
M05.769	Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems involvement
M05.771	Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems involvement
M05.772	Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement
M05.779	Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems involvement
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement
M05.80	Other rheumatoid arthritis with rheumatoid factor of unspecified site
M05.811	Other rheumatoid arthritis with rheumatoid factor of right shoulder
M05.812	Other rheumatoid arthritis with rheumatoid factor of left shoulder
M05.819	Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder
M05.821	Other rheumatoid arthritis with rheumatoid factor of right elbow
M05.822	Other rheumatoid arthritis with rheumatoid factor of left elbow
M05.829	Other rheumatoid arthritis with rheumatoid factor of unspecified elbow
M05.831	Other rheumatoid arthritis with rheumatoid factor of right wrist
M05.832	Other rheumatoid arthritis with rheumatoid factor of left wrist
M05.839	Other rheumatoid arthritis with rheumatoid factor of unspecified wrist
M05.841	Other rheumatoid arthritis with rheumatoid factor of right hand
M05.842	Other rheumatoid arthritis with rheumatoid factor of left hand
M05.849	Other rheumatoid arthritis with rheumatoid factor of unspecified hand
M05.851	Other rheumatoid arthritis with rheumatoid factor of right hip
M05.852	Other rheumatoid arthritis with rheumatoid factor of left hip
M05.859	Other rheumatoid arthritis with rheumatoid factor of unspecified hip
M05.861	Other rheumatoid arthritis with rheumatoid factor of right knee
M05.862	Other rheumatoid arthritis with rheumatoid factor of left knee
M05.869	Other rheumatoid arthritis with rheumatoid factor of unspecified knee
M05.871	Other rheumatoid arthritis with rheumatoid factor of right ankle and foot
M05.872	Other rheumatoid arthritis with rheumatoid factor of left ankle and foot
M05.879	Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot
M05.89	Other rheumatoid arthritis with rheumatoid factor of multiple sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00	Rheumatoid arthritis without rheumatoid factor, unspecified site
M06.011	Rheumatoid arthritis without rheumatoid factor, right shoulder

ICD-10 code	Description
M06.012	Rheumatoid arthritis without rheumatoid factor, left shoulder
M06.019	Rheumatoid arthritis without rheumatoid factor, unspecified shoulder
M06.021	Rheumatoid arthritis without rheumatoid factor, right elbow
M06.022	Rheumatoid arthritis without rheumatoid factor, left elbow
M06.029	Rheumatoid arthritis without rheumatoid factor, unspecified elbow
M06.031	Rheumatoid arthritis without rheumatoid factor, right wrist
M06.032	Rheumatoid arthritis without rheumatoid factor, left wrist
M06.039	Rheumatoid arthritis without rheumatoid factor, unspecified wrist
M06.041	Rheumatoid arthritis without rheumatoid factor, right hand
M06.042	Rheumatoid arthritis without rheumatoid factor, left hand
M06.049	Rheumatoid arthritis without rheumatoid factor, unspecified hand
M06.051	Rheumatoid arthritis without rheumatoid factor, right hip
M06.052	Rheumatoid arthritis without rheumatoid factor, left hip
M06.059	Rheumatoid arthritis without rheumatoid factor, unspecified hip
M06.061	Rheumatoid arthritis without rheumatoid factor, right knee
M06.062	Rheumatoid arthritis without rheumatoid factor, left knee
M06.069	Rheumatoid arthritis without rheumatoid factor, unspecified knee
M06.071	Rheumatoid arthritis without rheumatoid factor, right ankle and foot
M06.072	Rheumatoid arthritis without rheumatoid factor, left ankle and foot
M06.079	Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot
M06.08	Rheumatoid arthritis without rheumatoid factor, vertebrae
M06.09	Rheumatoid arthritis without rheumatoid factor, multiple sites
M06.20	Rheumatoid bursitis, unspecified site
M06.211	Rheumatoid bursitis, right shoulder
M06.212	Rheumatoid bursitis, left shoulder
M06.219	Rheumatoid bursitis, unspecified shoulder
M06.221	Rheumatoid bursitis, right elbow
M06.222	Rheumatoid bursitis, left elbow
M06.229	Rheumatoid bursitis, unspecified elbow
M06.231	Rheumatoid bursitis, right wrist
M06.232	Rheumatoid bursitis, left wrist
M06.239	Rheumatoid bursitis, unspecified wrist
M06.241	Rheumatoid bursitis, right hand
M06.242	Rheumatoid bursitis, left hand
M06.249	Rheumatoid bursitis, unspecified hand
M06.251	Rheumatoid bursitis, right hip
M06.252	Rheumatoid bursitis, left hip
M06.259	Rheumatoid bursitis, unspecified hip
M06.261	Rheumatoid bursitis, right knee
M06.262	Rheumatoid bursitis, left knee
M06.269	Rheumatoid bursitis, unspecified knee
M06.271	Rheumatoid bursitis, right ankle and foot
M06.272	Rheumatoid bursitis, left ankle and foot
M06.279	Rheumatoid bursitis, unspecified ankle and foot
M06.28	Rheumatoid bursitis, vertebrae
M06.29	Rheumatoid bursitis, multiple sites
M06.30	Rheumatoid nodule, unspecified site
M06.311	Rheumatoid nodule, right shoulder
M06.312	Rheumatoid nodule, left shoulder
M06.319	Rheumatoid nodule, unspecified shoulder
M06.321	Rheumatoid nodule, right elbow
M06.322	Rheumatoid nodule, left elbow
M06.329	Rheumatoid nodule, unspecified elbow

ICD-10 code	Description
M06.331	Rheumatoid nodule, right wrist
M06.332	Rheumatoid nodule, left wrist
M06.339	Rheumatoid nodule, unspecified wrist
M06.341	Rheumatoid nodule, right hand
M06.342	Rheumatoid nodule, left hand
M06.349	Rheumatoid nodule, unspecified hand
M06.351	Rheumatoid nodule, right hip
M06.352	Rheumatoid nodule, left hip
M06.359	Rheumatoid nodule, unspecified hip
M06.361	Rheumatoid nodule, right knee
M06.362	Rheumatoid nodule, left knee
M06.369	Rheumatoid nodule, unspecified knee
M06.371	Rheumatoid nodule, right ankle and foot
M06.372	Rheumatoid nodule, left ankle and foot
M06.379	Rheumatoid nodule, unspecified ankle and foot
M06.38	Rheumatoid nodule, vertebrae
M0639	Rheumatoid nodule, multiple sites
M06.80	Other specified rheumatoid arthritis, unspecified site
M06.811	Other specified rheumatoid arthritis, right shoulder
M06.812	Other specified rheumatoid arthritis, left shoulder
M06.819	Other specified rheumatoid arthritis, unspecified shoulder
M06.821	Other specified rheumatoid arthritis, right elbow
M06.822	Other specified rheumatoid arthritis, left elbow
M06.829	Other specified rheumatoid arthritis, unspecified elbow
M06.831	Other specified rheumatoid arthritis, right wrist
M06.832	Other specified rheumatoid arthritis, left wrist
M06.839	Other specified rheumatoid arthritis, unspecified wrist
M06.841	Other specified rheumatoid arthritis, right hand
M06.842	Other specified rheumatoid arthritis, left hand
M06.849	Other specified rheumatoid arthritis, unspecified hand
M06.851	Other specified rheumatoid arthritis, right hip
M06.852	Other specified rheumatoid arthritis, left hip
M06.859	Other specified rheumatoid arthritis, unspecified hip
M06.861	Other specified rheumatoid arthritis, right knee
M06.862	Other specified rheumatoid arthritis, left knee
M06.869	Other specified rheumatoid arthritis, unspecified knee
M06.871	Other specified rheumatoid arthritis, right ankle and foot
M06.872	Other specified rheumatoid arthritis, left ankle and foot
M06.879	Other specified rheumatoid arthritis, unspecified ankle and foot
M06.88	Other specified rheumatoid arthritis, vertebrae
M06.89	Other specified rheumatoid arthritis, multiple sites
M06.9	Rheumatoid arthritis, unspecified

Appendix H – RA drug codes

Drug	GPI Code[a]	HCPCS Code	NDC code	Medicare payment limit
TNFi		S9359		
ABATACEPT	66400010*	J0129	00003-2187-10	44.75/10MG
		C9230	00003-2188-11	
			0003-2188-21	
			00003-2188-31	
			0003-2188-51	
			0003-2188-91	
ADALIMUMAB	66270015*	J0135	0074-0554-01	861.447/20MG
			0074-0554-02	
			0074-0554-04	
			0074-0554-06	
			0074-0554-71	
			0074-0554-73	
			0074-0554-74	
			0074-2540-01	
			0074-2540-03	
			0074-3797-01	
			0074-3799-02	
			0074-3799-03	
			0074-3799-06	
			0074-3799-71	
			0074-4339-01	
			0074-4339-02	
			0074-4339-06	
			0074-4339-07	
			0074-4339-71	
			0074-4339-72	
			0074-4339-73	
			0074-4339-74	
			0074-6347-02	
			0074-9374-02	
			0074-9374-71	
ANAKINRA	66260010*	NA	66658-234-07	
			66658-234-07	
CERTOLIZUMAB	52505020*	J0717	50474-700-61	7.056/MG
		J0718	50474-700-62	

Drug	GPI Code[a]	HCPCS Code	NDC code	Medicare payment limit
		C9249	50474-710-79	
			50474-710-80	
			50474-710-81	
ETANERCEPT	66290030*	J1438	58406-425-34	
			58406-435-04	
			58406-445-04	
			58406-455-04	
GOLIMUMAB	66270040*	J1602	57894-070-01	24.787/MG
			57894-070-02	
			57894-070-89	
			57894-070-90	
			57894-071-01	
			57894-071-02	
			57894-071-89	
			57894-071-90	
			57894-350-01	
			57894-350-89	
INFLIXIMAB	52505040*	J1745 S9359	0069-0809-01	82.872/10MG
And biosimilars		EJ	57894-0030-01	
		J1745		
		Q5102		
		Q5103		
		Q5104	57894-0030-01	
RITUXIMAB	21353060*	J9310	50242-051-21	792.92/100MG
			50242-053-06	
TOFACITINIB	66603065100320	J8499	0069-0501-14	
			0069-0501-30	
			0069-1001-01	
			0069-1001-02	
			0069-1001-03	
			63539-012-02	
TOCILIZUMAB	66500070*	J3262	50242-135-01	4.103/MG
		C9264	50242-135-04	
			50242-136-01	
			50242-136-04	
			50242-137-01	
			50242-137-04	
			50242-138-01	

Appendix I – Excluded conditions

Condition	ICD9	ICD10
Ankylosing spondylitis	720.0X	M45
		M45.X
		M08.1
		M46.90
		M46.80
		M49.80
Crohn's disease	555.XX	K50.00
		K50.10
		K50.80
		K50.90
		K52.9
Juvenile idiopathic arthritis	714.3X	M08.00
		M08.3
		M08.40
Multiple sclerosis	340.XX	G35
Polyarteris nodosa	446.0X	M30.0
Psoriasis	696.0	L40.0
	696.1X	L40.1
		L40.2
		L40.3
		L40.4
		L40.8
		L40.54
		L40.59
Psoriatic arthritis	696.0X	L40.52
		L40.54
Spondyloarthropathy	721.9X	M47.819
		M47.10
Systemic lupus	710.0X	M32
erythematosus	695.4	M32.0
		M32.1
		M32.1X
		M32.8
		M32.9
		L93.0
Ulcerative colitis	556.XX	K51.80
		K51.20
		K51.30
		K51.40

Condition	ICD9	ICD10
		K51.50
		K51.00
		K51.80
		K51.811
		K51.812
		K51.814
		K51.818
		K51.819
		K51.90
		K51.911
		K51.912
		K51.913
		K51.914
		K51.918
		K51.919
		K52.9
		K52.89
Wegener's granulomatosis	446.4X	M31.3
		M31.30
		M31.31
HIV		B20
Organ transplant		
Malignancies		Any malignancy 140-172.9; 174-195.8; 200-208.9 / C00-C97
		Metastatic malignancy 196-199.1/C76-C80

Appendix J – Adherence criteria for IV drugs

		Month 0-6		Month 7-12	
drug	**HCPCS code**	**expected claims**	**minimum for adherence**	**expected claims**	**minimum for adherence**
ABATACEPT	J0129	8	6	6	5
ADALIMUMAB	J0135	13	10	13	10
CERTOLIZUMAB	J0717	8	6	6	5
CERTOLIZUMAB	J0718	8	6	6	5
ETANERCEPT	J1438	13	10	13	10
GOLIMUMAB	J1602	8	6	6	5
INFLIXIMAB	J1745	5	4	3	2
INFLIXIMAB	S9359	5	4	3	2
RITUXIMAB	J9310	2	2	2	2
TOCILIZUMAB	J3262	13	10	13	10
TOCILIZUMAB	C9264	13	10	13	10
TOFACITINIB	J8499	6	5	6	5

Appendix K – Time to discontinuation comparison per treatment line

2nd vs 3rd line

The NPAR1WAY Procedure

Wilcoxon Scores (Rank Sums) for Variable duration Classified by Variable line					
line	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
2	10442	84013859.0	82068899.0	268611.225	8045.76317
3	5276	39521762.0	41466722.0	268611.225	7490.85709
Average scores were used for ties.					

Wilcoxon Two-Sample Test					
				t Approximation	
Statistic	Z	Pr < Z	Pr > |Z|	Pr < Z	Pr > |Z|
39521762	-7.2408	<.0001	<.0001	<.0001	<.0001
Z includes a continuity correction of 0.5.					

Kruskal-Wallis Test		
Chi-Square	DF	Pr > ChiSq
52.4292	1	<.0001

3rd vs 4th line

The NPAR1WAY Procedure

Wilcoxon Scores (Rank Sums) for Variable duration Classified by Variable line					
line	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
3	5276	20265657.0	19687394.0	84682.0030	3841.10254
4	2186	7578796.0	8157059.0	84682.0030	3466.96981
Average scores were used for ties.					

Wilcoxon Two-Sample Test					
				t Approximation	
Statistic	Z	Pr < Z	Pr > |Z|	Pr < Z	Pr > |Z|
7578796	-6.8286	<.0001	<.0001	<.0001	<.0001
Z includes a continuity correction of 0.5.					

Kruskal-Wallis Test		
Chi-Square	DF	Pr > ChiSq
46.6303	1	<.0001

4th vs 5thline

The NPAR1WAY Procedure

Wilcoxon Scores (Rank Sums) for Variable duration Classified by Variable line					
line	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
4	2186	3306034.0	3216699.0	20126.6480	1512.36688
5	756	1023119.0	1112454.0	20126.6480	1353.33201

Average scores were used for ties.

Wilcoxon Two-Sample Test					
				t Approximation	
Statistic	Z	Pr < Z	Pr > |Z|	Pr < Z	Pr > |Z|
1023119	-4.4386	<.0001	<.0001	<.0001	<.0001

Z includes a continuity correction of 0.5.

Kruskal-Wallis Test		
Chi-Square	DF	Pr > ChiSq
19.7015	1	<.0001

5th vs 6th line

The NPAR1WAY Procedure

Wilcoxon Scores (Rank Sums) for Variable duration Classified by Variable line					
line	N	Sum of Scores	Expected Under H0	Std Dev Under H0	Mean Score
5	756	391557.0	392364.0	4285.44977	517.932540
6	281	146646.0	145839.0	4285.44977	521.871886

Average scores were used for ties.

Wilcoxon Two-Sample Test					
				t Approximation	
Statistic	Z	Pr < Z	Pr > |Z|	Pr < Z	Pr > |Z|
146646.0	0.1882	0.4254	0.8507	0.4254	0.8508

Z includes a continuity correction of 0.5.

Kruskal-Wallis Test		
Chi-Square	DF	Pr > ChiSq
0.0355	1	0.8506

Appendix L – Survival analysis results

Including rituximab
Second line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1175	LOGLOG	1086	1260	1321	LOGLOG	1232	1424
50	370	LOGLOG	354	392	471	LOGLOG	443	506
25	133	LOGLOG	126	140	180	LOGLOG	176	191

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	6635	4940	1695	25.55
2	non-TNFi	3807	2640	1167	30.65
Total		10442	7580	2862	27.41

Test of Equality over Strata

Test	Chi-Square	DF	Pr >Chi-Square
Log-Rank	34.7749	1	<.0001
Wilcoxon	46.7342	1	<.0001
-2Log(LR)	34.0832	1	<.0001

Third line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1374	LOGLOG	1245	1582	1438	LOGLOG	1332	1632
50	504	LOGLOG	462	561	441	LOGLOG	406	483
25	166	LOGLOG	155	181	186	LOGLOG	178	194

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	2404	1473	931	38.73
2	non-TNFi	2872	1635	1237	43.07
Total		5276	3108	2168	41.09

Test of Equality over Strata			
Test	**Chi-Square**	**DF**	**Pr > Chi-Square**
Log-Rank	0.3446	1	0.5572
Wilcoxon	0.191	1	0.6621
-2Log(LR)	3.3196	1	0.0685

Third line Cox Proportional Hazards Model

Variable	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Confidence Limits**	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.02159	0.03702	0.34	0.5598	0.979	0.91	1.052
Age	-0.03707	0.00966	14.7222	**0.0001**	.	.	.
Age2	0.0003349	0.0000951	12.3948	**0.0004**	.	.	.
Comorbidity score (ref=0)							
1	0.02626	0.05128	0.2623	0.6085	1.027	0.928	1.135
2+	0.11001	0.0816	1.8173	0.1776	1.116	0.951	1.31
Region (ref = North West)							
Northeast	0.08188	0.06393	1.6404	0.2003	1.085	0.958	1.23
South	0.0948	0.048	3.9011	**0.0483**	1.099	1.001	1.208
Unknown	0.28248	0.1602	3.1091	0.0779	1.326	0.969	1.816
West	0.02539	0.05752	0.1949	0.6589	1.026	0.916	1.148
Year of first TNFi (ref=2008)							
2009	0.14242	0.06253	5.1885	**0.0227**	1.153	1.02	1.303
2010	0.2151	0.06161	12.1881	**0.0005**	1.24	1.099	1.399
2011	0.29601	0.06347	21.7521	**<.0001**	1.344	1.187	1.523
2012	0.42511	0.06716	40.0613	**<.0001**	1.53	1.341	1.745
2013	0.4984	0.06487	59.0222	**<.0001**	1.646	1.45	1.869
2014	0.53872	0.07603	50.2104	**<.0001**	1.714	1.477	1.989
2015	0.87267	0.11462	57.9691	**<.0001**	2.393	1.912	2.996
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	0.00956	0.08515	0.0126	0.9106	1.01	0.854	1.193
Comprehensive	-0.08485	0.07215	1.3832	0.2396	0.919	0.798	1.058
Exclusive Provider Organization	0.05533	0.19823	0.0779	0.7802	1.057	0.717	1.559
High Deductible Health Plan	-0.16323	0.11909	1.8786	0.1705	0.849	0.673	1.073
Health maintenance Organization	0.04015	0.05636	0.5075	0.4762	1.041	0.932	1.163
Point of Service	0.04811	0.06593	0.5324	0.4656	1.049	0.922	1.194
Point of Service - Capitated	-0.02634	0.30342	0.0075	0.9308	0.974	0.537	1.765

Fourth line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1235	LOGLOG	1087	1452	1217	LOGLOG	1109	1497
50	402	LOGLOG	350	493	426	LOGLOG	379	489
25	144	LOGLOG	121	172	173	LOGLOG	155	185

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	799	468	331	41.43
2	non-TNFi	1387	761	626	45.13
Total		2186	1229	957	43.78

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.1346	1	0.7137
Wilcoxon	1.5662	1	0.2108
-2Log(LR)	0.0127	1	0.9101

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.04488	0.06051	0.5501	0.4583	0.956	0.849	1.076
Age	-0.02547	0.01591	2.5604	0.1096	.	.	.
Age2	0.0002418	0.0001564	2.3895	0.1222	.	.	.
Comorbidity score (ref=0)							
1	-0.01047	0.08421	0.0155	0.901	0.99	0.839	1.167
2+	0.14023	0.12363	1.2865	0.2567	1.151	0.903	1.466
Region (ref = North West)							
Northeast	0.05585	0.10297	0.2941	0.5876	1.057	0.864	1.294
South	0.08535	0.07741	1.2158	0.2702	1.089	0.936	1.268
Unknown	0.43728	0.23958	3.3312	0.068	1.548	0.968	2.477
West	0.00175	0.09216	0.0004	0.9848	1.002	0.836	1.2
Year of first TNFi (ref=2008)							
2009	-0.05789	0.09385	0.3805	0.5373	0.944	0.785	1.134
2010	0.09659	0.09569	1.0188	0.3128	1.101	0.913	1.329
2011	0.16443	0.09813	2.8079	0.0938	1.179	0.972	1.429
2012	0.05255	0.11039	0.2266	0.634	1.054	0.849	1.309
2013	0.19393	0.10556	3.3749	0.0662	1.214	0.987	1.493
2014	0.52038	0.12738	16.6894	**<.0001**	1.683	1.311	2.16
2015	0.5009	0.20605	5.9092	**0.0151**	1.65	1.102	2.471
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	-0.18155	0.14424	1.5842	0.2082	0.834	0.629	1.106
Comprehensive	0.02418	0.11578	0.0436	0.8346	1.024	0.816	1.285
Exclusive Provider Organization	-0.18309	0.38147	0.2304	0.6313	0.833	0.394	1.759
High Deductible Health Plan	-0.34453	0.20801	2.7435	0.0976	0.709	0.471	1.065
Health maintenance Organization	-0.05099	0.0867	0.3459	0.5565	0.95	0.802	1.126
Point of Service	-0.22967	0.10858	4.474	**0.0344**	0.795	0.642	0.983
Point of Service - Capitated	0.02127	0.50396	0.0018	0.9663	1.022	0.38	2.743

Fifth line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	653	LOGLOG	516	1106	979	LOGLOG	881	.
50	304	LOGLOG	248	371	339	LOGLOG	280	411
25	118	LOGLOG	87	156	156	LOGLOG	133	178

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	268	158	110	41.04
2	non-TNFi	488	267	221	45.29
Total		756	425	331	43.78

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	3.1774	1	0.0747
Wilcoxon	2.6913	1	0.1009
-2Log(LR)	3.8054	1	0.0511

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.15993	0.104	2.3645	0.1241	0.852	0.695	1.045
Age	-0.04873	0.02699	3.2601	0.071	.	.	.
Age2	0.0005446	0.0002753	3.9137	**0.0479**	.	.	.
Comorbidity score (ref=0)							
1	0.11592	0.14453	0.6433	0.4225	1.123	0.846	1.491
2+	0.06574	0.24868	0.0699	0.7915	1.068	0.656	1.739
Region (ref = North West)							
Northeast	0.01826	0.17513	0.0109	0.917	1.018	0.723	1.435
South	-0.18661	0.12999	2.0609	0.1511	0.83	0.643	1.071
Unknown	-0.173	0.59533	0.0844	0.7714	0.841	0.262	2.702
West	-0.18955	0.16011	1.4015	0.2365	0.827	0.604	1.132
Year of first TNFi (ref=2008)							
2009	0.18728	0.15149	1.5282	0.2164	1.206	0.896	1.623
2010	0.36435	0.15564	5.4803	0.0192	1.44	1.061	1.953
2011	0.38819	0.16398	5.6039	0.0179	1.474	1.069	2.033
2012	0.07126	0.203	0.1232	0.7256	1.074	0.721	1.599
2013	0.30298	0.18794	2.5988	0.1069	1.354	0.937	1.957
2014	0.15232	0.26371	0.3336	0.5635	1.165	0.695	1.953
2015	0.21681	0.51818	0.1751	0.6757	1.242	0.45	3.429
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	0.20848	0.24814	0.7059	0.4008	1.232	0.757	2.003
Comprehensive	-0.33541	0.22663	2.1904	0.1389	0.715	0.459	1.115
Exclusive Provider Organization	0.36514	0.51639	0.5	0.4795	1.441	0.524	3.964
High Deductible Health Plan	0.17674	0.45927	0.1481	0.7004	1.193	0.485	2.936
Health maintenance Organization	-0.15406	0.14784	1.0859	0.2974	0.857	0.642	1.145
Point of Service	0.23028	0.17327	1.7662	0.1839	1.259	0.896	1.768
Point of Service - Capitated	0.14464	1.01338	0.0204	0.8865	1.156	0.159	8.422

Sixth line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1150	LOGLOG	759	.	1013	LOGLOG	778	.
50	379	LOGLOG	206	759	397	LOGLOG	350	710
25	139	LOGLOG	90	190	156	LOGLOG	117	193

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	98	51	47	47.96
2	non-TNFi	183	86	97	53.01
Total		281	137	144	51.25

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.1556	1	0.6933
Wilcoxon	0.1672	1	0.6826
-2Log(LR)	0.0775	1	0.7807

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.07113	0.18825	0.1428	0.7055	0.931	0.644	1.347
Age	0.1497	0.07358	4.1397	**0.0419**	.	.	.
Age2	-0.00177	0.0007654	5.3601	**0.0206**	.	.	.
Comorbidity score (ref=0)							
1	-0.10536	0.28642	0.1353	0.713	0.9	0.513	1.578
2+	-0.05954	0.60789	0.0096	0.922	0.942	0.286	3.102
Region (ref = North West)							
Northeast	0.13572	0.3186	0.1815	0.6701	1.145	0.613	2.139
South	0.12092	0.24237	0.2489	0.6179	1.129	0.702	1.815
Unknown	-12.65014	569.61743	0.0005	0.9823	0	0	.
West	0.13504	0.28628	0.2225	0.6371	1.145	0.653	2.006
Year of first TNFi (ref=2008)							
2009	-0.13002	0.28066	0.2146	0.6432	0.878	0.507	1.522
2010	-0.05151	0.26258	0.0385	0.8445	0.95	0.568	1.589
2011	0.23421	0.29691	0.6222	0.4302	1.264	0.706	2.262
2012	-0.07412	0.39475	0.0353	0.8511	0.929	0.428	2.013
2013	-0.35093	0.43959	0.6373	0.4247	0.704	0.297	1.666
2014	-0.22967	0.53143	0.1868	0.6656	0.795	0.28	2.252
2015	-13.11555	3469	0	0.997	0	0	.
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	-0.47363	0.53305	0.7895	0.3743	0.623	0.219	1.77
Comprehensive	0.42252	0.38131	1.2278	0.2678	1.526	0.723	3.222
Exclusive Provider Organization	-1.26251	1.02619	1.5136	0.2186	0.283	0.038	2.114
High Deductible Health Plan	-1.13963	1.04733	1.184	0.2765	0.32	0.041	2.492
Health maintenance Organization	-1.04782	0.309	11.499	0.0007	0.351	0.191	0.643
Point of Service	-0.47088	0.31315	2.261	0.1327	0.624	0.338	1.154
Point of Service - Capitated	-13.40172	786.46855	0.0003	0.9864	0	0	.

Excluding rituximab
Second line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1175	LOGLOG	1086	1260	1255	LOGLOG	1147	1380
50	370	LOGLOG	354	392	455	LOGLOG	427	486
25	133	LOGLOG	126	140	156	LOGLOG	145	169

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	6635	4940	1695	25.55
2	non-TNFi	3267	2285	982	30.06
Total		9902	7225	2677	27.03

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	14.9073	1	0.0001
Wilcoxon	19.7824	1	<.0001
-2Log(LR)	11.792	1	0.0006

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.10317	0.02602	15.7169	**<.0001**	0.902	0.857	0.949
Age	-0.01673	0.00616	7.3696	**0.0066**	.	.	.
Age2	0.0001368	0.0000603	5.1411	**0.0234**	.	.	.
Comorbidity score (ref=0)							
1	0.02189	0.0335	0.427	0.5135	1.022	0.957	1.092
2+	0.15236	0.05258	8.3977	**0.0038**	1.165	1.051	1.291
Region (ref = North West)							
Northeast	-0.028	0.04132	0.4592	0.498	0.972	0.897	1.054
South	0.0754	0.0311	5.8787	**0.0153**	1.078	1.015	1.146
Unknown	-0.01157	0.10142	0.013	0.9092	0.989	0.81	1.206
West	0.08999	0.03755	5.7438	**0.0165**	1.094	1.017	1.178
Year of first TNFi (ref=2008)							
2009	0.08686	0.04075	4.5444	**0.033**	1.091	1.007	1.181
2010	0.11082	0.04036	7.5396	**0.006**	1.117	1.032	1.209
2011	0.27038	0.04144	42.5598	**<.0001**	1.31	1.208	1.421
2012	0.23928	0.04398	29.5953	**<.0001**	1.27	1.165	1.385
2013	0.2576	0.04314	35.663	**<.0001**	1.294	1.189	1.408
2014	0.42466	0.04764	79.4602	**<.0001**	1.529	1.393	1.679
2015	0.62477	0.07342	72.4124	**<.0001**	1.868	1.617	2.157
Plan type (ref = Preferred Provider Organization)	-0.0952	0.05277	3.2548	0.0712	0.909	0.82	1.008
Consumer Directed Health Plan	-0.04414	0.04683	0.8883	0.3459	0.957	0.873	1.049
Comprehensive	-0.32627	0.12553	6.7557	**0.0093**	0.722	0.564	0.923
Exclusive Provider Organization	0.09964	0.07554	1.7398	0.1872	1.105	0.953	1.281
High Deductible Health Plan	0.01579	0.03801	0.1726	0.6778	1.016	0.943	1.094
Health maintenance Organization	-0.02421	0.0454	0.2843	0.5939	0.976	0.893	1.067
Point of Service	0.12467	0.20099	0.3847	0.5351	1.133	0.764	1.68
Point of Service - Capitated	-0.0952	0.05277	3.2548	0.0712	0.909	0.82	1.008

Third line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1374	LOGLOG	1245	1582	1395	LOGLOG	1245	1530
50	504	LOGLOG	462	563	407	LOGLOG	378	448
25	166	LOGLOG	155	182	166	LOGLOG	154	176

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	2404	1473	931	38.73
2	non-TNFi	2499	1444	1055	42.22
Total		4903	2917	1986	40.51

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	4.7032	1	0.0301
Wilcoxon	4.7128	1	0.0299
-2Log(LR)	13.6033	1	0.0002

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	0.02415	0.03839	0.3957	0.5293	1.024	0.95	1.104
Age	-0.03759	0.00989	14.4469	**0.0001**	.	.	.
Age2	0.0003442	0.0000975	12.4727	**0.0004**	.	.	.
Comorbidity score (ref=0)							
1	0.02907	0.0528	0.3032	0.5819	1.029	0.928	1.142
2+	0.07468	0.08485	0.7746	0.3788	1.078	0.912	1.273
Region (ref = North West)							
Northeast	0.05491	0.06583	0.6957	0.4042	1.056	0.929	1.202
South	0.07589	0.04959	2.342	0.1259	1.079	0.979	1.189
Unknown	0.25068	0.1683	2.2184	0.1364	1.285	0.924	1.787
West	0.02114	0.05969	0.1255	0.7231	1.021	0.909	1.148
Year of first TNFi (ref=2008)							
2009	0.15694	0.06517	5.7997	**0.016**	1.17	1.03	1.329
2010	0.20142	0.06405	9.8883	**0.0017**	1.223	1.079	1.387
2011	0.28464	0.06606	18.5674	**<.0001**	1.329	1.168	1.513
2012	0.40657	0.06925	34.4733	**<.0001**	1.502	1.311	1.72
2013	0.48143	0.06664	52.1912	**<.0001**	1.618	1.42	1.844
2014	0.51429	0.0782	43.2494	**<.0001**	1.672	1.435	1.949
2015	0.87433	0.11635	56.4669	**<.0001**	2.397	1.908	3.011
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	-0.006	0.08697	0.0048	0.945	0.994	0.838	1.179
Comprehensive	-0.0637	0.07454	0.7302	0.3928	0.938	0.811	1.086
Exclusive Provider Organization	0.10703	0.2063	0.2692	0.6039	1.113	0.743	1.668
High Deductible Health Plan	-0.16465	0.12163	1.8324	0.1758	0.848	0.668	1.077
Health maintenance Organization	0.05106	0.05848	0.7623	0.3826	1.052	0.938	1.18
Point of Service	0.0542	0.06808	0.6337	0.426	1.056	0.924	1.206
Point of Service - Capitated	0.01684	0.30349	0.0031	0.9557	1.017	0.561	1.843

Fourth line

Kaplan Meier

Percent	TNFi				non-TNFi			
	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1235	LOGLOG	1087	1452	1053	LOGLOG	885	1263
50	402	LOGLOG	350	493	374	LOGLOG	328	414
25	144	LOGLOG	121	172	142	LOGLOG	118	160

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	799	468	331	41.43
2	non-TNFi	1175	677	498	42.38
Total		1974	1145	829	42

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	2.4185	1	0.1199
Wilcoxon	0.4462	1	0.5042
-2Log(LR)	5.2429	1	0.022

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	0.07171	0.0621	1.3337	0.2482	1.074	0.951	1.213
Age	-0.03163	0.01679	3.5491	0.0596	.	.	.
Age2	0.0002918	0.000164	3.1646	0.0753	.	.	.
Comorbidity score (ref=0)							
1	0.01807	0.08669	0.0434	0.8349	1.018	0.859	1.207
2+	0.19755	0.12917	2.3389	0.1262	1.218	0.946	1.569
Region (ref = North West)							
Northeast	0.02787	0.10709	0.0677	0.7947	1.028	0.834	1.268
South	0.03212	0.08013	0.1607	0.6885	1.033	0.883	1.208
Unknown	0.28744	0.26845	1.1465	0.2843	1.333	0.788	2.256
West	-0.04347	0.09623	0.2041	0.6515	0.957	0.793	1.156
Year of first TNFi (ref=2008)							
2009	-0.07757	0.09846	0.6208	0.4307	0.925	0.763	1.122
2010	0.05877	0.09956	0.3484	0.555	1.061	0.873	1.289
2011	0.12084	0.1008	1.4369	0.2306	1.128	0.926	1.375
2012	0.03623	0.11482	0.0996	0.7523	1.037	0.828	1.299
2013	0.11646	0.10823	1.1577	0.2819	1.124	0.909	1.389
2014	0.50976	0.13039	15.2853	**<.0001**	1.665	1.289	2.15
2015	0.38716	0.21876	3.1323	0.0768	1.473	0.959	2.261
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	-0.13383	0.15118	0.7837	0.376	0.875	0.65	1.176
Comprehensive	-0.01128	0.12048	0.0088	0.9254	0.989	0.781	1.252
Exclusive Provider Organization	-0.01593	0.38169	0.0017	0.9667	0.984	0.466	2.08
High Deductible Health Plan	-0.41585	0.21737	3.6598	0.0557	0.66	0.431	1.01
Health maintenance Organization	-0.07619	0.09004	0.7161	0.3974	0.927	0.777	1.105
Point of Service	-0.28589	0.11205	6.5104	**0.0107**	0.751	0.603	0.936
Point of Service - Capitated	-0.03679	0.50445	0.0053	0.9419	0.964	0.359	2.591

Fifth line

Kaplan Meier

	TNFi				non-TNFi			
Percent	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	653	LOGLOG	516	1106	885	LOGLOG	640	1313
50	304	LOGLOG	248	370	280	LOGLOG	239	333
25	118	LOGLOG	87	155	133	LOGLOG	109	150

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	268	158	110	41.04
2	non-TNFi	411	241	170	41.36
Total		679	399	280	41.24

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	0.0805	1	0.7767
Wilcoxon	0.0506	1	0.822
-2Log(LR)	0.0896	1	0.7647

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	-0.01755	0.10611	0.0274	0.8686	0.983	0.798	1.21
Age	-0.05474	0.02811	3.7915	0.0515	.	.	.
Age2	0.0005922	0.0002895	4.184	0.0408	.	.	.
Comorbidity score (ref=0)							
1	0.11384	0.14939	0.5807	0.446	1.121	0.836	1.502
2+	-0.14763	0.2891	0.2608	0.6096	0.863	0.49	1.52
Region (ref = North West)							
Northeast	-0.00293	0.1814	0.0003	0.9871	0.997	0.699	1.423
South	-0.22292	0.13399	2.7677	0.0962	0.8	0.615	1.041
Unknown	0.18664	0.59511	0.0984	0.7538	1.205	0.375	3.869
West	-0.20196	0.16547	1.4898	0.2223	0.817	0.591	1.13
Year of first TNFi (ref=2008)							
2009	0.16775	0.15704	1.1411	0.2854	1.183	0.869	1.609
2010	0.38048	0.16264	5.4727	**0.0193**	1.463	1.064	2.012
2011	0.37198	0.16958	4.8114	**0.0283**	1.451	1.04	2.023
2012	0.09308	0.21015	0.1962	0.6578	1.098	0.727	1.657
2013	0.39826	0.19349	4.2368	**0.0396**	1.489	1.019	2.176
2014	0.15235	0.27248	0.3126	0.5761	1.165	0.683	1.987
2015	0.13242	0.51873	0.0652	0.7985	1.142	0.413	3.155
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	0.26111	0.25514	1.0473	0.3061	1.298	0.787	2.141
Comprehensive	-0.27408	0.23648	1.3433	0.2465	0.76	0.478	1.209
Exclusive Provider Organization	0.20048	0.59502	0.1135	0.7362	1.222	0.381	3.922
High Deductible Health Plan	0.15704	0.46077	0.1162	0.7332	1.17	0.474	2.887
Health maintenance Organization	-0.13618	0.15159	0.807	0.369	0.873	0.648	1.175
Point of Service	0.26547	0.17688	2.2526	0.1334	1.304	0.922	1.844
Point of Service - Capitated	0.02324	1.01401	0.0005	0.9817	1.024	0.14	7.468

Sixth line

Kaplan Meier

	TNFi				non-TNFi			
Percent	Point Estimate	95% Confidence Interval			Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)		Transform	[Lower	Upper)
75	1150	LOGLOG	759	.	951	LOGLOG	415	.
50	379	LOGLOG	206	759	323	LOGLOG	183	394
25	139	LOGLOG	113	190	117	LOGLOG	84	146

Summary of the Number of Censored and Uncensored Values

Stratum	group	Total	Failed	Censored	Percent Censored
1	TNFi	98	51	47	47.96
2	non-TNFi	137	74	63	45.99
Total		235	125	110	46.81

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	1.3219	1	0.2503
Wilcoxon	1.3866	1	0.239
-2Log(LR)	1.732	1	0.1882

Cox Proportional Hazards Model

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Confidence Limits	
Drug group (ref = TNFi cyclers)							
non-TNFi swappers	0.27762	0.20423	1.8479	0.174	1.32	0.885	1.97
Age	0.19459	0.07805	6.2153	**0.0127**	.	.	.
Age2	-0.00218	0.0008216	7.0561	**0.0079**	.	.	.
Comorbidity score (ref=0)							
1	-0.255	0.28643	0.7926	0.3733	0.775	0.442	1.359
2+	-0.05162	0.61793	0.007	0.9334	0.95	0.283	3.188
Region (ref = North West)							
Northeast	0.16559	0.33415	0.2456	0.6202	1.18	0.613	2.272
South	0.11614	0.26001	0.1995	0.6551	1.123	0.675	1.87
Unknown	-12.79163	557.67253	0.0005	0.9817	0	0	.
West	0.28647	0.30809	0.8646	0.3525	1.332	0.728	2.436
Year of first TNFi (ref=2008)							
2009	-0.06237	0.31643	0.0388	0.8438	0.94	0.505	1.747
2010	0.3333	0.28193	1.3977	0.2371	1.396	0.803	2.425
2011	0.33788	0.30731	1.2088	0.2716	1.402	0.768	2.56
2012	-0.06289	0.40023	0.0247	0.8751	0.939	0.429	2.058
2013	-0.02594	0.44365	0.0034	0.9534	0.974	0.408	2.325
2014	-0.26082	0.53482	0.2378	0.6258	0.77	0.27	2.198
2015	-13.13722	3189	0	0.9967	0	0	.
Plan type (ref = Preferred Provider Organization)							
Consumer Directed Health Plan	-0.38884	0.53897	0.5205	0.4706	0.678	0.236	1.949
Comprehensive	0.4223	0.38439	1.207	0.2719	1.525	0.718	3.24
Exclusive Provider Organization	-0.50905	1.03651	0.2412	0.6233	0.601	0.079	4.584
High Deductible Health Plan	0.56996	1.04625	0.2968	0.5859	1.768	0.227	13.744
Health maintenance Organization	-1.11019	0.38191	8.4501	**0.0037**	0.329	0.156	0.697
Point of Service	-0.2301	0.31924	0.5195	0.471	0.794	0.425	1.485
Point of Service - Capitated	-13.82519	726.43432	0.0004	0.9848	0	0	.

Appendix M – Costs: TNFi vs non-TNFi

	Variable	N	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max	p
TNFi	Drug costs_06mon	6,626	12,709	7,321	4	7,795	11,821	16,421	150,267	0.023
non-TNFi	Drug costs_06mon	3,816	13,053	7,604	0	8,366	12,512	16,407	73,905	
TNFi	Other costs_06mon	6,626	6,138	13,962	0	1,215	2,730	5,857	433,647	<0.001
non-TNFi	Other costs_06mon	3,816	8,228	16,709	0	2,080	3,941	7,814	307,414	
TNFi	Drug costs _712mon	6,626	7,683	8,732	0	-	6,246	12,561	141,679	0.237
non-TNFi	Drug costs _712mon	3,816	7,886	7,960	0	-	7,233	13,113	84,903	
TNFi	Other costs _712mon	6,626	5,100	13,502	0	275	1,742	4,690	408,690	<0.001
non-TNFi	Other costs _712mon	3,816	7,474	19,140	0	852	2,761	6,578	505,420	
TNFi	Drug costs _1yr	6,626	20,392	14,514	4	9,222	18,906	27,729	291,946	0.058
non-TNFi	Drug costs _1yr	3,816	20,939	13,678	0	10,775	20,322	28,412	151,091	
TNFi	Other costs _1yr	6,626	11,238	22,798	0	2,190	5,118	11,731	745,918	<0.001
non-TNFi	Other costs _1yr	3,816	15,702	29,226	0	3,731	7,581	16,112	723,371	

Adherent month 1-6	Group	Variable	N	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max	p
No	TNFi	Drug costs_06mon	3,073	8,756	5,819	3.5	4,825	7638.9	11138	73855	<0.001
No	non-TNFi	Drug costs_06mon	1,803	9,711	6,669	17	5,041	8,861	13,266	66,497	
No	TNFi	Other costs_06mon	3,073	6,767	17,718	-	1,014	2,484	5,846	433,647	0.002
No	non-TNFi	Other costs_06mon	1,803	8,423	18,232	-	1,618	3,495	7,539	307,414	
Yes	TNFi	Drug costs_06mon	3,553	16,128	6,743	150	11,785	14,665	18,986	150,267	0.668
Yes	non-TNFi	Drug costs_06mon	2,013	16,046	7,130	21	11,952	14,421	18,468	73,905	
Yes	TNFi	Other costs_06mon	3,553	5,594	9,562	-	1,427	2,908	5,860	223,595	<0.001
Yes	non-TNFi	Other costs_06mon	2,013	8,053	15,219	-	2,545	4,304	8,013	305,051	

Adherent month 7-12	Group	Variable	N	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max	p
No	TNFi	Drug costs _712mon	4,428	3,721	5,770	0	0	0	6,917	59,198	<0.001
No	non-TNFi	Drug costs _712mon	2,491	4,393	6,374	0	0	0	7,628	84,903	
No	TNFi	Other costs _712mon	4,428	4,779	13,835	0	0	1,026	3,883	408,690	<0.001
No	non-TNFi	Other costs _712mon	2,491	7,176	21,225	0	127	1,901	5,748	505,420	
No	TNFi	line2totalpay_1yr	4,428	14,977	11,003	4	6,492	12,465	20,772	133,053	<0.001
No	non-TNFi	line2totalpay_1yr	2,491	16,170	11,948	0	7,125	14,008	22,875	151,091	
No	TNFi	othertotalpay_1yr	4,428	11,117	24,996	0	1,753	4,369	11,006	745,918	<0.001
No	non-TNFi	othertotalpay_1yr	2,491	15,844	32,771	0	2,936	6,733	15,500	723,371	
Yes	TNFi	Drug costs_712mon	2,198	15,665	8,214	175	10,958	13,586	18,796	141,679	<0.001
Yes	non-TNFi	Drug costs_712mon	1,325	14,455	6,324	28	10,642	13,293	17,001	70,150	

Adherent month 7-12	Group	Variable	N	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max	p
Yes	TNFi	Other costs_712mon	2,198	5,746	12,784	0	1,430	2,973	5,930	404,588	<0.001
Yes	non-TNFi	Other costs_712mon	1,325	8,035	14,418	0	2,152	4,076	7,659	208,996	
Yes	TNFi	Drug costs _1yr	2,198	31,301	14,600	325	22,851	27,836	36,820	291,946	0.0035
Yes	non-TNFi	Drug costs _1yr	1,325	29,906	12,138	3,950	22,584	27,646	34,749	121,280	
Yes	TNFi	Other costs _1yr	2,198	11,482	17,554	56	3,353	6,551	12,852	408,179	<0.001
Yes	non-TNFi	Other costs _1yr	1,325	15,435	21,008	139	5,096	8,966	16,825	222,226	

Appendix N – Drug specific costs

LINE2_drg	Variable	N	Mean	StdDev	Min	25th Pctl	Median	75th Pctl	Max
ABATACEPT	Drug costs_06mon	2,073	13,244	7,228	0	8,837	12,520	16,418	73,905
	Other costs_06mon	2,073	7,852	14,057	0	2,270	4,120	7,912	215,271
	Drug costs _712mon	2,073	7,756	7,676	0	-	7,273	12,468	70,150
	Other costs _712mon	2,073	7,479	19,668	0	1,032	2,914	6,878	505,420
	Drug costs _1yr	2,073	21,000	13,276	0	11,519	19,984	27,811	121,280
	Other costs _1yr	2,073	15,331	26,803	0	4,036	7,867	16,355	509,699
ADALIMUMAB	Drug costs_06mon	2,732	12,873	7,277	305	7,700	12,015	16,792	62,378
	Other costs_06mon	2,732	5,553	11,848	0	1,053	2,340	5,120	249,259
	Drug costs _712mon	2,732	7,900	9,214	0	0	5,577	13,042	70,365
	Other costs _712mon	2,732	4,543	12,332	0	124	1,484	4,051	404,588
	Drug costs _1yr	2,732	20,773	14,892	305	8,799	18,785	29,048	126,436
	Other costs _1yr	2,732	10,096	18,601	0	1,905	4,438	10,195	408,179
ANAKINRA	Drug costs_06mon	16	8,158	6,299	49	3,078	7,051	11,147	22,610
	Other costs_06mon	16	12,807	29,704	1,428	2,815	5,059	7,969	123,519
	Drug costs _712mon	16	4,885	7,171	0	0	0	9,514	20,336
	Other costs _712mon	16	14,674	34,135	0	151	2,657	16,250	138,311
	Drug costs _1yr	16	13,043	13,113	49	3,078	7,051	20,424	40,671
	Other costs _1yr	16	27,482	63,416	1,428	5,471	7,058	19,451	261,830
CERTOLIZUMAB	Drug costs_06mon	738	12,870	6,494	150	8,435	12,145	16,448	60,000
	Other costs_06mon	738	6,804	16,263	0	1,397	2,869	6,168	242,057
	Drug costs _712mon	738	6,638	7,098	0	0	5,439	11,380	48,000
	Other costs _712mon	738	6,758	20,356	0	274	2,054	5,733	408,690
	Drug costs _1yr	738	19,507	11,912	325	9,742	18,652	26,015	108,000
	Other costs _1yr	738	13,562	32,656	0	2,387	5,892	13,022	650,747
ETANERCEPT	Drug costs_06mon	1,612	12,000	6,207	10	7,283	11,748	15,883	33,001
	Other costs_06mon	1,612	5,708	13,664	0	1,113	2,403	5,303	250,678
	Drug costs _712mon	1,612	7,244	7,517	0	0	6,109	12,429	44,964
	Other costs _712mon	1,612	4,545	11,143	0	228	1,542	4,100	254,085
	Drug costs _1yr	1,612	19,243	12,361	10	8,453	18,679	26,730	66,912
	Other costs _1yr	1,612	10,253	19,687	0	2,038	4,552	10,276	275,990
GOLIMUMAB	Drug costs_06mon	855	12,591	8,235	4	7,787	11,501	15,764	150,267
	Other costs_06mon	855	6,386	18,514	0	1,115	2,669	5,677	433,647
	Drug costs _712mon	855	7,548	8,677	0	0	7,262	12,320	141,679
	Other costs _712mon	855	5,079	14,965	0	318	1,636	4,340	312,271
	Drug costs _1yr	855	20,139	15,696	4	9,372	19,690	26,856	291,946
	Other costs _1yr	855	11,464	30,541	-	2,072	4,818	11,754	745,918
INFLIXIMAB	Drug costs_06mon	689	13,693	9,168	408	8,212	11,744	17,300	76,374
	Other costs_06mon	689	8,447	12,892	0	2,994	4,814	8,877	201,792
	Drug costs _712mon	689	9,140	10,652	0	0	7,085	12,908	130,058
	Other costs _712mon	689	6,855	11,456	0	1,612	3,751	7,515	127,718
	Drug costs _1yr	689	22,833	17,949	408	11,579	19,089	28,772	206,432
	Other costs _1yr	689	15,303	19,839	0	5,243	9,105	17,910	216,501
RITUXIMAB	Drug costs_06mon	539	16,469	8,713	21	11,584	13,577	21,368	61,015

LINE2_drg	Variable	N	Mean	StdDev	Min	25th Pctl	Median	75th Pctl	Max
TOCILIZUMAB	Other costs_06mon	539	10,457	23,640	0	2,318	4,137	8,719	305,051
	Drug costs _712mon	539	8,437	8,952	0	0	7,699	13,559	41,518
	Other costs _712mon	539	7,776	16,187	0	1,116	2,851	7,413	166,417
	Drug costs _1yr	539	24,906	14,119	182	13,574	24,244	30,880	94,912
	Other costs _1yr	539	18,233	33,190	0	3,917	7,654	19,446	421,973
	Drug costs_06mon	640	11,984	7,466	269	6,975	11,395	16,224	66,497
	Other costs_06mon	640	8,903	20,471	31	2,202	3,931	7,511	307,414
	Drug costs _712mon	640	8,365	8,280	0	0	7,736	13,756	84,903
	Other costs _712mon	640	8,487	22,444	0	1,107	3,156	6,943	415,957
	Drug costs _1yr	640	20,348	14,272	269	9,099	19,188	28,331	151,091
	Other costs _1yr	640	17,390	37,411	31	4,082	7,925	15,460	723,371
TOFACITINIB	Drug costs_06mon	548	10,363	6,603	0	4,791	11,160	15,149	29,088
	Other costs_06mon	548	6,536	11,219	0	1,200	2,796	6,939	131,879
	Drug costs _712mon	548	7,368	7,564	0	0	6,862	14,184	32,408
	Other costs _712mon	548	5,764	14,349	0	0	1,503	4,775	144,527
	Drug costs _1yr	548	17,731	13,053	0	5,559	17,803	28,767	56,161
	Other costs _1yr	548	12,300	19,537	0	2,234	5,534	13,041	159,796

Adherent 0-6mon	LINE2_drg	Obs	Variable	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max
0	ABATACEPT	820	Drug costs_06mon	9,776	6,198	0	5,373	8,436	13,216	37,486
			Other costs_06mon	8,246	17,187	0	1,534	3,541	7,771	215,271
	ADALIMUMAB	1,180	Drug costs_06mon	7,654	4,645	305	4,357	6,870	10,150	46,304
			Other costs_06mon	5,849	13,612	0	828	2,079	4,799	249,259
	ANAKINRA	10	Drug costs_06mon	4,401	3,168	49	1,614	4,175	6,230	10,331
			Other costs_06mon	16,716	37,625	1,428	2,271	5,282	7,572	123,519
	CERTOLIZUMAB	448	Drug costs_06mon	10,494	5,987	1,434	6,412	9,413	12,736	60,000
			Other costs_06mon	7,849	19,737	0	1,406	3,051	6,834	242,057
	ETANERCEPT	726	Drug costs_06mon	7,298	4,239	10	4,214	6,798	9,403	32,431
			Other costs_06mon	7,053	18,876	0	977	2,361	5,609	250,678
	GOLIMUMAB	589	Drug costs_06mon	11,842	7,647	4	6,497	10,124	15,986	73,855
			Other costs_06mon	6,698	20,625	0	1,176	2,810	5,983	433,647
	INFLIXIMAB	130	Drug costs_06mon	6,926	6,090	408	3,197	5,791	8,628	43,906
			Other costs_06mon	10,100	21,638	0	1,834	4,278	9,442	201,792
	RITUXIMAB	92	Drug costs_06mon	10,339	4,845	182	6,683	11,211	12,838	33,608
			Other costs_06mon	9,834	19,534	0	1,518	2,947	5,618	96,718
	TOCILIZUMAB	557	Drug costs_06mon	11,712	7,677	269	6,458	10,781	16,204	66,497
			Other costs_06mon	9,054	21,325	31	2,130	3,864	7,613	307,414
	TOFACITINIB	324	Drug costs_06mon	6,094	4,624	0	2,133	6,278	9,550	17,300
			Other costs_06mon	7,131	13,060	0	1,070	2,715	7,135	131,879
1	ABATACEPT	1,253	Drug costs_06mon	15,513	6,950	1,595	11,660	14,183	17,763	73,905
			Other costs_06mon	7,593	11,558	157	2,749	4,425	8,000	143,370
	ADALIMUMAB	1,552	Drug costs_06mon	16,842	6,353	4,986	12,182	15,362	19,759	62,378
			Other costs_06mon	5,328	10,305	0	1,234	2,546	5,307	223,595
	ANAKINRA	6	Drug costs_06mon	14,421	5,067	10,609	11,090	11,662	18,895	22,610
			Other costs_06mon	6,292	4,173	2,236	3,358	5,059	8,367	13,672
	CERTOLIZUMAB	290	Drug costs_06mon	16,540	5,463	150	12,791	15,235	18,515	38,650
			Other costs_06mon	5,189	8,226	79	1,370	2,605	5,467	69,846
	ETANERCEPT	886	Drug costs_06mon	15,852	4,735	4,731	12,320	14,782	18,481	33,001
			Other costs_06mon	4,607	6,732	0	1,244	2,414	5,207	79,977
			Drug costs_06mon	5,693	12,652	6	1,060	2,224	4,952	136,167
	INFLIXIMAB	559	Other costs_06mon	15,266	9,050	1,185	9,566	13,206	18,442	76,374
			Drug costs_06mon	8,063	9,793	518	3,148	5,105	8,729	108,888
	RITUXIMAB	447	Other costs_06mon	17,730	8,800	21	12,019	14,360	22,931	61,015
			Drug costs_06mon	10,586	24,417	7	2,554	4,328	9,619	305,051
	TOCILIZUMAB	83	Other costs_06mon	13,809	5,556	2,682	10,561	12,799	16,512	36,099
			Drug costs_06mon	7,888	13,456	1,393	2,750	4,037	6,772	102,024
	TOFACITINIB	224	Other costs_06mon	16,539	3,343	8,458	14,166	15,904	18,320	29,088
			Drug costs_06mon	5,675	7,774	0	1,384	2,972	6,659	60,839

Adherent 612	LINE2_drg	Obs	Variable	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max
0	ABATACEPT	1,196	Drug costs _712mon	3,420	5,319	0	0	0	5,996	31,765
			Other costs _712mon	7,351	23,545	0	98	1,709	5,729	505,420
			Drug costs _1yr	15,271	10,771	0	7,181	13,347	20,500	79,668
			Other costs _1yr	15,687	31,375	0	2,936	6,789	15,905	509,699
	ADALIMUMAB	1,894	Drug costs _712mon	3,600	5,899	0	0	0	6,548	48,753
			Other costs _712mon	4,252	10,507	0	0	927	3,443	144,977
			Drug costs _1yr	14,851	11,131	305	6,226	12,232	20,354	79,904
			Other costs _1yr	9,925	18,533	0	1,580	3,787	9,651	259,078
	ANAKINRA	11	Drug costs _712mon	702	2,330	0	0	0	0	7,727
			Other costs _712mon	18,615	40,835	0	0	2,749	19,564	138,311
			Drug costs _1yr	5,722	5,313	49	1,614	5,061	7,872	18,930
			Other costs _1yr	34,244	76,220	1,428	5,019	7,197	21,213	261,830
	CERTOLIZUMAB	548	Drug costs _712mon	3,889	5,504	0	0	0	7,877	48,000
			Other costs _712mon	6,736	22,226	0	0	1,342	5,475	408,690
			Drug costs _1yr	15,806	10,303	1,434	8,316	13,912	21,768	108,000
			Other costs _1yr	13,921	36,375	0	2,069	5,158	13,346	650,747
	ETANERCEPT	1,100	Drug costs _712mon	3,360	4,838	0	0	0	6,695	24,440
			Other costs _712mon	4,532	12,598	0	0	940	3,580	254,085
			Drug costs _1yr	13,674	9,327	10	5,885	11,815	19,294	54,378
			Other costs _1yr	10,667	21,972	0	1,666	4,181	10,639	275,990
	GOLIMUMAB	655	Drug costs _712mon	5,622	7,195	0	0	1,764	10,905	59,198
			Other costs _712mon	5,052	15,748	0	17	1,402	4,217	312,271
			Drug costs _1yr	17,908	13,272	4	7,352	15,000	26,091	133,053
			Other costs _1yr	11,668	33,258	0	2,017	4,914	11,812	745,918
	INFLIXIMAB	231	Drug costs _712mon	651	1,658	0	0	0	0	10,887
			Other costs _712mon	4,863	11,189	0	0	500	5,623	80,327
			Drug costs _1yr	11,944	9,887	408	4,870	9,535	16,500	72,396
			Other costs _1yr	14,827	23,547	0	2,867	7,228	16,886	216,501
	RITUXIMAB	289	Drug costs _712mon	2,067	4,545	0	0	0	0	31,631
			Other costs _712mon	6,397	14,462	0	151	1,648	5,745	164,860
			Drug costs _1yr	17,977	10,974	182	11,568	14,231	23,602	73,034
			Other costs _1yr	18,621	38,969	0	3,132	6,681	19,179	421,973
	TOCILIZUMAB	585	Drug costs _712mon	7,793	8,211	0	0	6,659	12,803	84,903
			Other costs _712mon	8,496	22,902	0	910	3,030	7,105	415,957
			Drug costs _1yr	19,646	14,273	269	8,633	18,295	27,721	151,091
			Other costs _1yr	17,355	38,111	31	3,983	8,019	15,500	723,371
	TOFACITINIB	410	Drug costs _712mon	4,117	5,497	0	0	0	8,458	18,762
			Other costs _712mon	5,024	13,222	0	0	1,013	3,832	144,527
			Drug costs _1yr	12,839	10,852	0	2,697	9,596	21,537	39,581
			Other costs _1yr	11,692	18,487	0	1,974	5,072	11,912	159,796
1	ABATACEPT	877	Drug costs _712mon	13,669	6,331	28	9,870	12,350	16,235	70,150
			Other costs _712mon	7,654	12,598	0	2,424	4,187	7,716	208,996
			Drug costs _1yr	28,812	12,358	3,950	21,326	26,277	33,534	121,280
			Other costs _1yr	14,844	18,866	172	5,433	9,357	16,831	222,226

Adherent 612	LINE2_drg	Obs	Variable	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max
	ADALIMUMAB	838	Drug costs _712mon	17,620	7,867	8,374	12,044	15,200	21,348	70,365
			Other costs _712mon	5,202	15,681	0	1,168	2,483	5,240	404,588
			Drug costs _1yr	34,159	13,588	12,132	24,705	30,691	40,058	126,436
			Other costs _1yr	10,484	18,760	150	2,814	5,588	11,485	408,179
	ANAKINRA	5	Drug costs _712mon	14,087	5,032	8,200	10,829	13,011	18,061	20,336
			Other costs _712mon	6,005	8,014	381	1,554	2,565	5,612	19,913
			Drug costs _1yr	29,152	10,121	18,808	21,919	25,131	39,230	40,671
			Other costs _1yr	12,605	12,438	2,617	5,923	6,919	13,979	33,585
	CERTOLIZUMAB	190	Drug costs _712mon	14,564	4,873	175	10,999	12,718	18,146	31,904
			Other costs _712mon	6,824	13,643	129	1,622	3,453	6,432	126,329
			Drug costs _1yr	30,183	9,583	325	23,467	27,231	35,941	57,270
			Other costs _1yr	12,526	18,100	361	3,667	7,149	12,442	148,972
	ETANERCEPT	512	Drug costs _712mon	15,588	5,057	4,731	11,767	14,323	18,382	44,964
			Other costs _712mon	4,571	7,080	0	1,218	2,413	4,648	80,543
			Drug costs _1yr	31,210	9,185	9,462	24,259	28,424	36,428	66,912
			Other costs _1yr	9,364	13,509	56	2,734	5,314	9,962	141,743
	GOLIMUMAB	200	Drug costs _712mon	13,853	10,040	7,962	10,549	11,888	15,342	141,679
			Other costs _712mon	5,168	12,082	125	962	2,214	5,022	144,809
			Drug costs _1yr	27,442	20,207	13,656	21,309	23,586	29,643	291,946
			Other costs _1yr	10,798	19,161	347	2,277	4,651	11,618	180,808
	INFLIXIMAB	458	Drug costs _712mon	13,422	10,708	890	7,085	10,650	17,000	130,058
			Other costs _712mon	7,860	11,469	390	2,684	4,481	7,996	127,718
			Drug costs _1yr	28,325	18,591	2,187	17,062	23,873	35,393	206,432
			Other costs _1yr	15,543	17,701	2,133	6,356	9,994	18,368	204,138
	RITUXIMAB	250	Drug costs _712mon	15,800	6,910	2,354	12,217	13,559	16,180	41,518
			Other costs _712mon	9,370	17,874	132	2,042	3,977	8,596	166,417
			Drug costs _1yr	32,915	13,088	4,765	25,029	28,813	37,431	94,912
			Other costs _1yr	17,785	24,964	139	4,913	9,100	19,672	180,230
	TOCILIZUMAB	55	Drug costs _712mon	14,447	6,403	5,838	10,785	13,880	16,800	39,137
			Other costs _712mon	8,401	16,977	1,004	2,095	3,871	6,299	113,743
			Drug costs _1yr	27,818	12,037	11,730	21,595	25,427	32,353	75,235
			Other costs _1yr	17,765	29,217	2,618	5,539	7,849	14,881	182,699
	TOFACITINIB	138	Drug costs _712mon	17,027	3,554	7,032	14,738	16,175	18,875	32,408
			Other costs _712mon	7,961	17,135	0	1,246	3,306	6,473	134,892

Adherent 612	LINE2_drg	Obs	Variable	Mean	Std Dev	Min	25th Pctl	Median	75th Pctl	Max
			Drug costs _1yr	32,266	6,656	13,610	27,875	30,882	36,758	56,161
			Other costs _1yr	14,107	22,347	194	3,146	6,888	14,328	142,901

Mean drug costs in descending order

Drug costs for the first 6 months

adherent06	LINE2_drg	Mean
0	GOLIMUMAB	11841.8
	TOCILIZUMAB	11711.8
	CERTOLIZUMAB	10494.2
	RITUXIMAB	10339
	ABATACEPT	9775.6
	ADALIMUMAB	7653.6
	ETANERCEPT	7297.9
	INFLIXIMAB	6925.5
	TOFACITINIB	6094
	ANAKINRA	4400.6
1	RITUXIMAB	17730.1
	ADALIMUMAB	16841.6
	CERTOLIZUMAB	16539.6
	TOFACITINIB	16538.5
	ETANERCEPT	15852.2
	ABATACEPT	15513.1
	INFLIXIMAB	15266.4
	ANAKINRA	14421
	GOLIMUMAB	14249.9
	TOCILIZUMAB	13808.7

Drug costs for the second 6 months

adherent612	LINE2_drg	Mean
0	TOCILIZUMAB	7792.6
	GOLIMUMAB	5622.1
	TOFACITINIB	4116.7
	CERTOLIZUMAB	3889.4
	ADALIMUMAB	3599.7
	ABATACEPT	3419.8
	ETANERCEPT	3360.1
	RITUXIMAB	2067.4
	ANAKINRA	702.4
	INFLIXIMAB	651.1
1	ADALIMUMAB	17619.7
	TOFACITINIB	17027
	RITUXIMAB	15800.3
	ETANERCEPT	15587.6
	CERTOLIZUMAB	14563.8
	TOCILIZUMAB	14447.4
	ANAKINRA	14087
	GOLIMUMAB	13853.2
	ABATACEPT	13669.3
	INFLIXIMAB	13421.6

Annual drug costs

adherent612	LINE2_drg	Mean
0	TOCILIZUMAB	19646
	RITUXIMAB	17977.3
	GOLIMUMAB	17908.4
	CERTOLIZUMAB	15805.8
	ABATACEPT	15271
	ADALIMUMAB	14850.7
	ETANERCEPT	13673.7
	TOFACITINIB	12838.9
	INFLIXIMAB	11943.8
	ANAKINRA	5721.5
1	ADALIMUMAB	34159.1
	RITUXIMAB	32914.7
	TOFACITINIB	32265.7
	ETANERCEPT	31209.6
	CERTOLIZUMAB	30183.3
	ANAKINRA	29151.6
	ABATACEPT	28811.6
	INFLIXIMAB	28324.7
	TOCILIZUMAB	27817.5
	GOLIMUMAB	27442.1

Appendix O – Drug specific costs per Deyo score

In descending cost order

	adherent	LINE2_drg	Variable	Mean	LINE2_drg	Variable	Mean
DEYO =0	0	INFLIXIMAB	Other costs _06mon	8,169	ANAKINRA	othertotalpay_612mon	11,998
		TOCILIZUMAB	Other costs _06mon	6,926	TOCILIZUMAB	othertotalpay_612mon	7,469
		ABATACEPT	Other costs _06mon	6,659	CERTOLIZUMAB	othertotalpay_612mon	5,574
		CERTOLIZUMAB	Other costs _06mon	6,337	ABATACEPT	othertotalpay_612mon	5,458
		ETANERCEPT	Other costs _06mon	5,899	RITUXIMAB	othertotalpay_612mon	4,594
		TOFACITINIB	Other costs _06mon	5,777	ETANERCEPT	othertotalpay_612mon	4,137
		ANAKINRA	Other costs _06mon	5,724	TOFACITINIB	othertotalpay_612mon	4,003
		RITUXIMAB	Other costs _06mon	5,517	ADALIMUMAB	othertotalpay_612mon	3,750
		ADALIMUMAB	Other costs _06mon	5,134	GOLIMUMAB	othertotalpay_612mon	3,584
		GOLIMUMAB	Other costs _06mon	4,595	INFLIXIMAB	othertotalpay_612mon	3,310
	adherent	**LINE2_drg**	**Variable**	**Mean**	**LINE2_drg**	**Variable**	**Mean**
	1	RITUXIMAB	Other costs _06mon	8,770	TOCILIZUMAB	othertotalpay_612mon	8,240
		INFLIXIMAB	Other costs _06mon	7,230	RITUXIMAB	othertotalpay_612mon	7,302
		ABATACEPT	Other costs _06mon	6,424	INFLIXIMAB	othertotalpay_612mon	7,167
		GOLIMUMAB	Other costs _06mon	5,414	TOFACITINIB	othertotalpay_612mon	6,737
		TOCILIZUMAB	Other costs _06mon	5,066	ABATACEPT	othertotalpay_612mon	6,380
		ADALIMUMAB	Other costs _06mon	4,832	CERTOLIZUMAB	othertotalpay_612mon	5,385
		TOFACITINIB	Other costs _06mon	4,589	ADALIMUMAB	othertotalpay_612mon	4,814
		CERTOLIZUMAB	Other costs _06mon	4,397	GOLIMUMAB	othertotalpay_612mon	4,238
		ETANERCEPT	Other costs _06mon	4,020	ETANERCEPT	othertotalpay_612mon	4,044
		ANAKINRA	Other costs _06mon	2,797	ANAKINRA	othertotalpay_612mon	1,473
	adherent	**LINE2_drg**	**Variable**	**Mean**	**LINE2_drg**	**Variable**	**Mean**
DEYO =1	0	ANAKINRA	Other costs _06mon	27,556	ANAKINRA	othertotalpay_612mon	26128.7
		INFLIXIMAB	Other costs _06mon	19,181	INFLIXIMAB	othertotalpay_612mon	10381.4
		RITUXIMAB	Other costs _06mon	17,876	TOCILIZUMAB	othertotalpay_612mon	10242.2
		TOCILIZUMAB	Other costs _06mon	14,308	ABATACEPT	othertotalpay_612mon	10080.5
		ETANERCEPT	Other costs _06mon	11,958	RITUXIMAB	othertotalpay_612mon	7645.9
		ABATACEPT	Other costs _06mon	11,730	CERTOLIZUMAB	othertotalpay_612mon	7630.8
		CERTOLIZUMAB	Other costs _06mon	10,523	GOLIMUMAB	othertotalpay_612mon	6465.3
		GOLIMUMAB	Other costs _06mon	10,135	TOFACITINIB	othertotalpay_612mon	6118.6
		TOFACITINIB	Other costs _06mon	8,405	ADALIMUMAB	othertotalpay_612mon	6047.4
		ADALIMUMAB	Other costs _06mon	7,578	ETANERCEPT	othertotalpay_612mon	5547.6
	adherent	**LINE2_drg**	**Variable**	**Mean**	**LINE2_drg**	**Variable**	**Mean**
	1	ADALIMUMAB	Other costs _06mon	18,172	RITUXIMAB	othertotalpay_612mon	14,812
		TOFACITINIB	Other costs _06mon	17,072	CERTOLIZUMAB	othertotalpay_612mon	13,440
		ABATACEPT	Other costs _06mon	16,099	ANAKINRA	othertotalpay_612mon	10,733
		RITUXIMAB	Other costs _06mon	15,803	ABATACEPT	othertotalpay_612mon	9,389
		ETANERCEPT	Other costs _06mon	15,606	INFLIXIMAB	othertotalpay_612mon	9,040
		ANAKINRA	Other costs _06mon	15,311	TOFACITINIB	othertotalpay_612mon	9,036
		INFLIXIMAB	Other costs _06mon	15,190	TOCILIZUMAB	othertotalpay_612mon	7,058
		CERTOLIZUMAB	Other costs _06mon	14,889	ADALIMUMAB	othertotalpay_612mon	6,879
		GOLIMUMAB	Other costs _06mon	13,798	ETANERCEPT	othertotalpay_612mon	6,147
		TOCILIZUMAB	Other costs _06mon	11,876	GOLIMUMAB	othertotalpay_612mon	5,742

	adherent	LINE2_drg	Variable	Mean	LINE2_drg	Variable	Mean
DEYO≥2	0	GOLIMUMAB	Other costs _06mon	27,315	GOLIMUMAB	othertotalpay_612mon	22052.5
		CERTOLIZUMAB	Other costs _06mon	20,630	CERTOLIZUMAB	othertotalpay_612mon	21147.4
		TOFACITINIB	Other costs _06mon	19,830	ABATACEPT	othertotalpay_612mon	18485.9
		TOCILIZUMAB	Other costs _06mon	18,193	TOCILIZUMAB	othertotalpay_612mon	14923.8
		RITUXIMAB	Other costs _06mon	18,044	TOFACITINIB	othertotalpay_612mon	14754.1
		ABATACEPT	Other costs _06mon	15,620	INFLIXIMAB	othertotalpay_612mon	12147.6
		ADALIMUMAB	Other costs _06mon	13,739	RITUXIMAB	othertotalpay_612mon	12111
		ETANERCEPT	Other costs _06mon	11,804	ETANERCEPT	othertotalpay_612mon	8207.7
		ANAKINRA	Other costs _06mon	6,487	ADALIMUMAB	othertotalpay_612mon	7769.3
		INFLIXIMAB	Other costs _06mon	4,870	ANAKINRA	othertotalpay_612mon	0
	adherent	**LINE2_drg**	**Variable**	**Mean**	**LINE2_drg**	**Variable**	**Mean**
	1	TOCILIZUMAB	Other costs _06mon	25,679	GOLIMUMAB	othertotalpay_612mon	41,694
		RITUXIMAB	Other costs _06mon	14,680	RITUXIMAB	othertotalpay_612mon	15,925
		ABATACEPT	Other costs _06mon	14,441	ABATACEPT	othertotalpay_612mon	15,218
		INFLIXIMAB	Other costs _06mon	12,905	TOCILIZUMAB	othertotalpay_612mon	14,345
		TOFACITINIB	Other costs _06mon	10,544	INFLIXIMAB	othertotalpay_612mon	13,773
		GOLIMUMAB	Other costs _06mon	9,859	TOFACITINIB	othertotalpay_612mon	13,561
		ADALIMUMAB	Other costs _06mon	9,398	ETANERCEPT	othertotalpay_612mon	8,669
		ETANERCEPT	Other costs _06mon	9,372	CERTOLIZUMAB	othertotalpay_612mon	7,330
		CERTOLIZUMAB	Other costs _06mon	8,458	ADALIMUMAB	othertotalpay_612mon	6,729
		ANAKINRA	Other costs _06mon	8,367	ANAKINRA	othertotalpay_612mon	5,612