Measuring switchability using observational data

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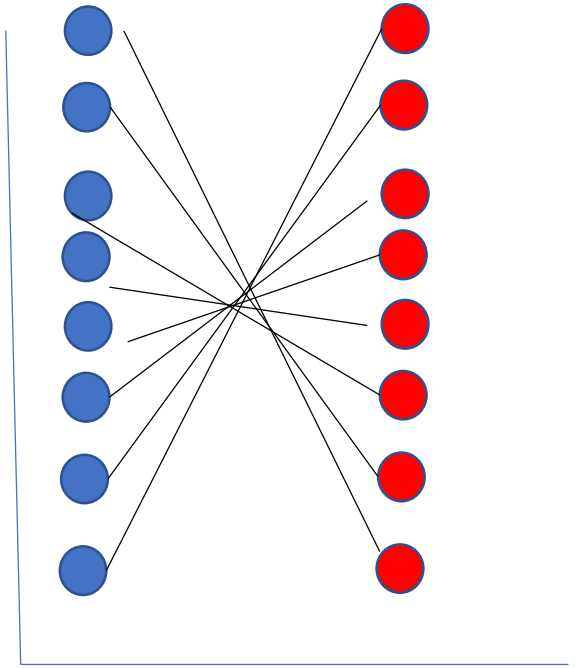
Prescribability, Switchability, Interchangeability, Substitution : Terminology

- **Prescribability**
  - If a biosimilar product is approved then it can be prescribed. The approval is based on by showing that population risk/benefit ratio the originator and biosimilar is equivalent
  - Typical clinical trial design: parallel

- **Switchability, Interchangeability, Substitution**
  - Legally they are slightly different terms but in the following I do not make any distinctions among them
  - Statistically speaking a biosimilar product can be substituted with the originator if the risk/benefit ratios within subjects are equivalent (i.e., conditionally)



The population means are equivalent but there are large differences individually

Measuring Switchability

- In the EU labeling a biosimilar product to be interchangeable is the responsibility of individual member states.
- In the US labeling a biosimilar product to be interchangeable is a legal duty of the FDA. The FDA issued a guideline for qualifying a biosimilar product to be interchangeable.
- The Guideline suggests:
  - at least four period studies (like TRTR-RTRT) design
  - patients instead of healthy volunteers
  - rich sampling for PK and PD endpoints
  - standard 80- 125% criterion
  - options for requesting post-marketing data to support for a designation of interchangeability

Comments on the FDA Guideline

- Many questioned the clinical relevance and sensitivity of the proposed PK/PD approach.
  - For example, assume that the incidence of immunogenicity is 10% to 20%, where immunogenicity is associated with a clinically significant halving of the AUC. Still the doubling of clinically significant immunogenicity would mean only 5% reduction in the AUC.
  - Safety/Efficacy differences resulting from structural differences may not be reflected in PK differences
  - Immunogenic responses to a biologic may first occur only after extended exposure of months
- Therefore long-term comparative safety/efficacy studies are suggested using real-world clinical data.

Assessment of the impact of switching from clinical records

- Retrospective analysis is an attractive option.
- But, for obvious reasons, such data are scarce even in the EU.
- A recent survey by McKinnon et al., identified only 10 studies[1].
- There are many limitations of these studies including relatively short observation times (6-12 months), poor reporting (many of them are abstracts) and lack of statistical analysis.
- Therefore, still an open question: the value of easily available routine clinical data to assess the clinical impact of switching.
- To answer this question, we investigated an alternative question, the consequence of switching between two biologicals.

[1] McKinnon et al., Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. BioDrugs (2018) 32:27–52

Rheumathoid arthritis (RA) and the between-product switching

- RA is a chronic, progressive immune-mediated inflammatory disease
- Six biologicals (abbreviated as ETA, ADA, RTX, INF, TCZ, GOL) are available for the treatment. By mode of action they are classified as TNF and non-TNF antagonists.
- During the course of the therapy (which lasts for several years, sometimes lifelong) it is common in clinical practice to switch patients from an original product to another due to loss of efficiency or intolerability. But there is no clear clinical direction how to switch from one to another.
- For example, one treatment pathway is like ETA→ADA while another pathway is TCZ→RTX→INF→ETA . Or maybe just ETA→.
- An open question: what is the optimal sequence?
  - Does the pre-treatment with drug A influence the follow-up B drug effect ?
  - Following a TNF antagonist another TNF antagonist or a non-TNF antagonist should be administered ?

The concept

- Registry data with biologicals go back to several years.
- The original question was how registry data can be used to assess the originator--> biosimilar (or vice versa) switching.
- But because with biosimilars there is no long term experience, we have investigated an alternative question: the effect of switching from a TNF antagonist to a non-TNF antagonist (or vice versa).
- Statistically the problem is very similar except we have to adjust for the individual drug effects.
- The clinical endpoint is failure time with a given product.

Descriptive statistics of the database

Characteristics	Total sample (N=540, treatment periods=1108)
Age, mean (SD)	53.6 (12.8)
Woman, n (%)	456 (84.4)
Disease duration (in years) at first therapy (N=525), mean (SD)	12.1 (9.2)
Rheumatoid factor (N=521 patients)	
Negative, n (%)	194 (37.2)
Positive, n (%)	327 (62.8)
Anti-CCP (N=524 patients)	
Negative, n (%)	183 (35.0)
Positive, n (%)	341 (65.0)
Corticosteroid use (N=1099 treatment periods)	
No, n (%)	674 (61.3)
Yes, n (%)	425 (38.7)
sDMARD (N=1105 treatment periods)	
No, n (%)	230 (20.8)
Yes, n (%)	875 (79.2)
First bDMARD (N=540)	
TNF-α, n (%)	515 (92.6)
Non-TNF-α, n (%)	25 (7.4)
Gap more than 30 days since last bDMARD therapy (N=1108 treatment periods)	
No (including first therapy), n (%)	974 (87.9)
Yes, n (%)	134 (12.1)

Abbreviations: bDMARD, biological disease-modifying antirheumatic drug; CCP, cyclic citrullinated peptide; SD, standard deviation; sDMARD, synthetic disease-modifying antirheumatic drug; TNF-α, tumor necrosis factor-alpha.

Clinical records of an RA treatment center collected over 8 yrs.

Chronic disease

Biological predictors

Co-medications

Typically they start with TNF antagonists

Sometimes there are treatment gaps (pregnancy, other diseases..)

Survival statisistics

```
        failure _d:  event == 1 2 3
  analysis time _t:  (ende-origin)
            origin:  time starte
 exit on or before:  time .
                id:  id
```

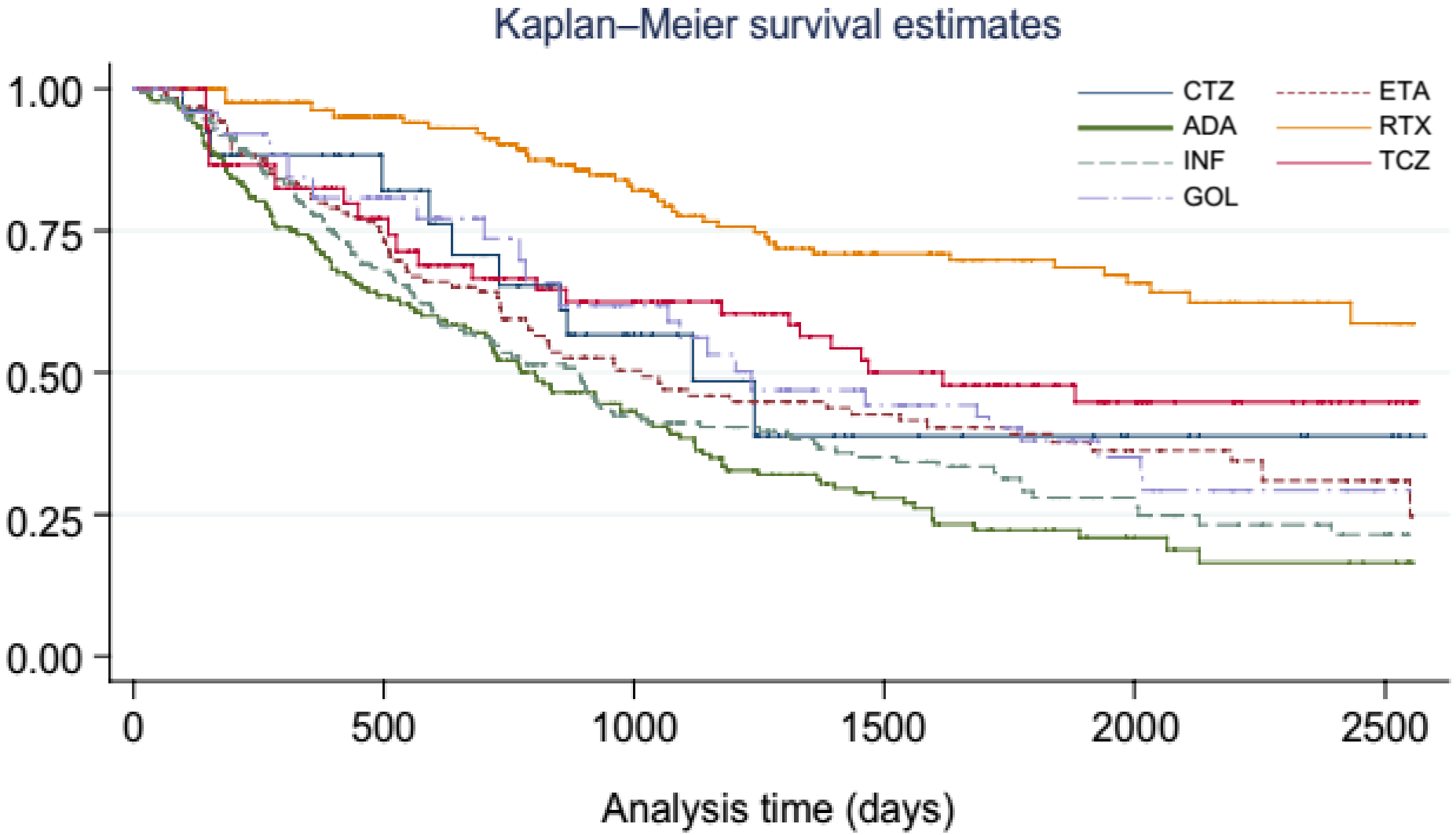
Treatment failure can be due inefficiency, side effect or other

Category	total	per subject: mean	min	median	max
no. of subjects	545				
no. of records	1118	2.051376	1	2	7
(first) entry time		.0422018	0	0	23
(final) exit time		1305.782	1	1246	2955
subjects with gap	257				
time on gap if gap	35198	95.38753	1	16	1834
time at risk	676430	1241.156	1	1198	2844
failures	668	1.225688	0	1	7

Half of the subjects had at least one switch

Half of the subjects were followed at least 4 yrs

Subject with 7 failures


Kaplan–Meier survival estimates
1.00
0.75
0.50
0.25
0.00
0
500
1000
1500
2000
2500
Analysis time (days)
CTZ
ADA
INF
GOL
ETA
RTX
TCZ

How to assess the impact of switching

- We define the clinical effect as the length of the period during which the patients' symptoms are controlled.
- If there is a „switching" effect then the effect B in sequence A_1B_2 will not be the same as in sequence B_1A_2. The difference could be due two factors:
  - The failure time depends on the number of the previous failures („repeat")
  - The „switching" can be measured by defining an additional variable called Switch: isTNF(i+1) != isTNF(i))

- The increased hazard of failure due to switching was estimated using proportional hazard regression with multiple failure times. We used Stata (ver 15.1) for modelling.

Results (failure for any reason)

_t	Haz. Ratio	Robust Std. Err.	z	P>|z|
rep	1.039872	.055652	0.73	0.465
dmard	.7472842	.0660572	-3.30	0.001
gender	.7723142	.1019827	-1.96	0.050
steroid	1.001691	.0865882	0.02	0.984
rf	.9779592	.0903808	-0.24	0.809
ccp	.8847248	.0835174	-1.30	0.194
dislspan	1.006112	.0040965	1.50	0.134
age	1.007021	.0029166	2.42	0.016
drugi				
ENB	.8288599	.1854187	-0.84	0.401
HUM	1.081818	.235333	0.36	0.718
MAB	.4493283	.1100911	-3.27	0.001
REM	1.068662	.2343177	0.30	0.762
ROA	.5156165	.1535876	-2.22	0.026
SIM	.7225061	.1957892	-1.20	0.230
Switch	.9191428	.1052737	-0.74	0.462

No significant period („repeat") effect

Co-treatment with DMARD (MTX) is very effective

Being woman is an advantage

The failure rate depends on the age of the patient

Some mABs are more effective than the reference CMZ

It does not matter that TNF antagonist is followed by another TNF antagonist or non-TNF antagonist

Results – failure due only to inefficiency

(Std. Err. adjusted for 507 clusters in id)

_t	Haz. Ratio	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
rep	1.071414	.0639162	1.16	0.248	.9531867	1.204305
Switch	.7936131	.1065461	-1.72	0.085	.610002	1.032491
dmard	.8868789	.1091198	-0.98	0.329	.6968418	1.128741
gender	.8897585	.156052	-0.67	0.505	.6309319	1.254763
steroid	.9476189	.1103703	-0.46	0.644	.7542116	1.190623
rf	1.011066	.1294355	0.09	0.931	.7867011	1.29942
ccp	.8377297	.1073097	-1.38	0.167	.6517313	1.07681
dislspan	.9972813	.006094	-0.45	0.656	.9854086	1.009297
age	1.006768	.0036615	1.85	0.064	.9996174	1.01397
drugi						
ENB	1.256379	.4398831	0.65	0.514	.632555	2.495417
HUM	1.919847	.6611119	1.89	0.058	.9775746	3.770366
MAB	.4996748	.1863481	-1.86	0.063	.24057	1.037848
REM	1.517686	.5255258	1.20	0.228	.7699071	2.991752
ROA	.6822183	.2909624	-0.90	0.370	.2957267	1.573824
SIM	.8121269	.3390363	-0.50	0.618	.3583235	1.840656

The risk of failure can be decreased if the next drug is selected with a different mode of action (TNF- non-TNF)

Results – failure due to side effects

(Std. Err. adjusted for 507 clusters in id)

_t	Haz. Ratio	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
rep	.9013093	.0923535	-1.01	0.311	.7373177	1.101775
Switch	1.009691	.2004068	0.05	0.961	.6842884	1.489834
dmard	.60116	.1059162	-2.89	0.004	.4256179	.8491026
gender	.6252885	.1463926	-2.01	0.045	.3951819	.9893817
steroid	1.128999	.191536	0.72	0.474	.8096296	1.574349
rf	.877203	.1543909	-0.74	0.457	.6212774	1.238553
ccp	.9191725	.1625971	-0.48	0.634	.6498657	1.300081
dislspan	1.016689	.0075426	2.23	0.026	1.002012	1.03158
age	1.005112	.0062549	0.82	0.413	.9929275	1.017447
drugi						
ENB	.7223537	.2928625	-0.80	0.422	.3263239	1.599009
HUM	.6399839	.2602618	-1.10	0.272	.2884108	1.420125
MAB	.4933315	.2175599	-1.60	0.109	.2078537	1.1709
REM	1.021625	.3931734	0.06	0.956	.4805136	2.172087
ROA	.5496019	.2751055	-1.20	0.232	.2060514	1.465955
SIM	.9665624	.4392009	-0.07	0.940	.3966873	2.355111

← Not related
← Not related
← Strong protection
← Strong protection

Conclusions

- The clinical relevance of PK or PD data to demonstrate interchangeability has been questioned by many stakeholders during the discussion of the FDA Draft Guideline.
- The hazard ratio of treatment failure is a clinically meaningful and sensitive parameter. We could detect the effects of well-known risk factors (co-treatment, gender) from a relatively small clinical database. These important variables can be obtained from health-insurance databases.
- However it is important to note that failure can be happen due to multiple reasons and switching was selective in this regard.

Conclusions - Methodology

- In this presentation switching means a TNF--> not TNF switch but Originator-->Biosimilar switching could have been analyzed exactly in the same way.
- Our data allow to estimate to power for such an observational study and points out some unresolved methodological questions
  - Bias due to unbalance
    - More RT or RT_1T_2 sequence than TR
    - How to handle between treatment gaps
    - Censoring subjects only with one observation (Day <30)

Acknowledgment

Our clinical partners (who were keenly interested in the TNF--> non-TNF switching)

Determinants of biological drug survival in rheumatoid arthritis: evidence from a Hungarian rheumatology center over 8 years of retrospective data

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Objective: To compare drug survival of biological therapies in patients with rheumatoid arthritis (RA), and analyze the determinants of discontinuation probabilities and switches to other biological therapies.

Materials and methods: Consecutive RA patients initiating first biological treatment in one rheumatology center between 2006 and 2013 were included. Log-rank test was used to analyze the differences between the survival curves of different biological drugs. Cox regression was applied to analyze the discontinuation due to inefficacy, the occurrence of adverse events, or to any reasons.

Results: A total of 540 patients were included in the analysis. The most frequently used first-line biological treatments were infliximab (N=176, 33%), adalimumab (N=150, 28%), and etanercept (N=132, 24%). Discontinuation of first tumor necrosis factor-alpha (TNF-α) treatment was observed for 347 (64%) patients, due to inefficacy (n=209, 60%), adverse events (n=103, 30%), and other reasons (n=35, 10%). Drug survival rates for TNF-α and non-TNF-α therapies were significantly different, and were in favor of non-TNF-α therapies. Every additional number of treatment significantly increased the risk of inefficacy by 27% (p<0.001) and of adverse events by 35% (p=0.002). After the discontinuation of the initial TNF-α treatment, switching to rituximab and tocilizumab was associated with significantly longer treatment duration than switching to a second TNF-α. The non-TNF-α therapies resulted in significantly longer treatment duration, due to both less adverse events and longer maintenance of effectiveness.

Conclusion: Non-TNF-α therapies resulted in significantly longer treatment duration, and lost their effectiveness later. Increase in the number of switches significantly increased the risk of discontinuation of any biological therapy.

Keywords: rheumatoid arthritis, biologicals, drug survival, switch, registry