CO148

TIME IN REMISSION AS AN ALTERNATIVE OUTCOME MEASURE FOR ANKYLOSING SPONDYLITIS: A 14-YEAR PROSPECTIVE STUDY OF 900 USERS OF ANTI-TNF

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Background

Estimating the unobserved disease activity between physician appointments, time in remission (TIR) can be used to describe patient health state over time. We have recently validated TIR (https://www.medevio.cz/tir-calculator/) as an effective outcome measure for rheumatoid arthritis patients (1). This study aimed to introduce TIR in ankylosing spondylitis.

Methods

The cohort of ankylosing spondylitis patients from the Czech ATTRA-AS registry initiating anti-TNF between 2003 and 2016 was described previously (2), patient were followed for up to 31 visits (14 years on the first anti-TNF therapy). We selected records created after 2013, the year when ASDAS started to be universally collected (3) (**Table 1**). Point remission and sustained remission were defined as ASDAS-CRP < 1.3 in one or both of two consecutive visits, respectively (4). TIR (0% to 100%) was interpolated between each two ASDAS-CRP values measured at two consecutive visits as previously described (1) (Stata code available with **Figure 1**). Years spent in remission were calculated by multiplying TIR with the length of the follow-up; i.e. [% × years].

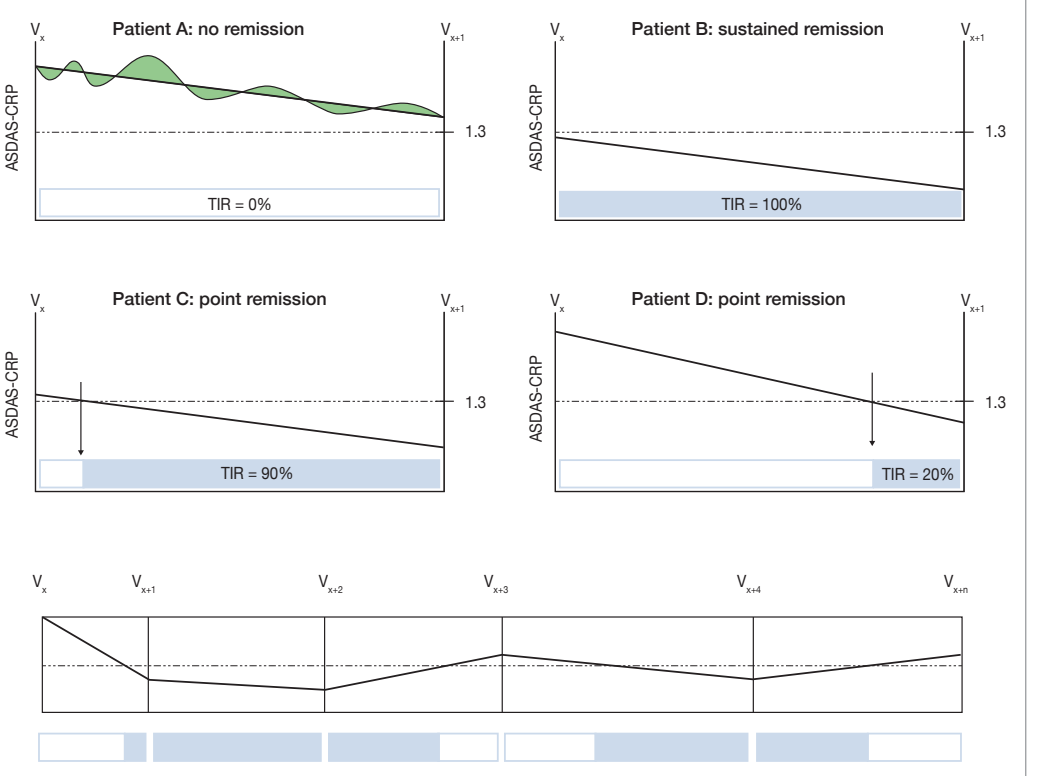
Spearman correlation coefficients were calculated between CRP, BASFI, BASDAI, HAQ, SF-36 bodily pain, EQ-5D utility and WPAI work impairment in the panel (longitudinal) dataset. Additionally, we used TIR, point remission and sustained remission to predict EQ5D utility and work impairment in a training sample via mixed effect clustered linear regression (5,6). Adjusted R^2 and mean squared error (MSE) of the prediction were calculated in the test set (split 70/30).

Table 1. Baseline characteristics of the cohort

Patients	927 (100%)
Male gender	672 (72%)
Previous disease duration [years]	7.39 ± 7.75
Enrolled [calendar years]	2003 to 2016
Follow-up [calendar years]	2013 to 2016
No DMARDs prior to biologics	333 (36%)
1 DMARD prior to biologics	345 (38%)
2 DMARDs prior to biologics	178 (19%)
3 DMARDs prior to biologics	45 (5%)
4 DMARDs prior to biologics	11 (1%)
ASDAS-CRP	3.99 ± 0.80
CRP [mg/L]	24.58 ± 22.17
Radiological stage 0	43 (8%)
Radiological stage 3	119 (21%)
Radiological stage 4	166 (30%)
Radiological stage 5	228 (41%)
BASFI	5.21 ± 2.21
BASDAI	6.21 ± 1.67
HAQ	1.14 ± 0.55
SF-36 Bodily pain [%]	29.31 ± 15.69
EQ-5D utility	0.33 ± 0.31
Complete disability	85 (9%)
WPAI work impairment [%]	0.53 ± 0.22
Panel observations	11007

The cohort of ankylosing spondylitis patients from the Czech ATTRA-AS registry initiating their first anti-TNF between 2003 and 2016 was described previously (2). We selected records created after 2013, the year when ASDAS started to be universally collected. Parameters are presented as count (%) or mean ± standard deviation. ASDAS: Ankylosing Spondylitis Disease Activity Score based on the CRP: C-reactive protein, BASFI: Bath Ankylosing Functional Index, BADAI: Bath Ankylosing Spondylitis. Disease Activity Index, HAQ: Health Assessment. Questionnaire, EQ5D: EuroQoL 5 Dimension questionnaire-derived utility, Work impairment was calculated from the WPAI: Work Productivity and Activity Impairment Questionnaire, SF-36: 36-Item Short Form Survey

Figure 1. Time in remission (TIR) calculated based on disease activity (ASDAS-CRP) measured at two consecutive visits



Patient A: the true disease activity (squiggly line) remains unobserved between visit x (Vx) and visit x+1 (Vx+1), but it can be approximated with linear interpolation (straight line) using disease activity on visit x and visit x+1. Patient A did not achieve remission in either of the two visits, and thus, TIR = 0%. Patient B achieved remission on both visits and hence spent 100% of the time in remission; this corresponds to sustained remission. Patient C did not achieve remission on visit x but did achieve remission on the next visit; this corresponds to point remission. TIR in patient C is high because the patient achieved remission early after visit x. Patient D, on the other hand, achieved remission long after visit x. Their state would also be rated as point remission, but this patient had a ASDAS-CRP > 1.3 most of the time. Although patients C and D would normally both be categorized as being in point remission, their health states are importantly different, and TIR can capture this difference. The entire follow-up of each patient can be conceived as a zig-zag line, which is interpolated between the measurements at individual visits. Periods are spent in remission, not in remission or partly in remission. TIR: time in remission, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score based on the C-reactive protein

TIR is calculated based on Euclidean similarity, see the Stata code bellow:

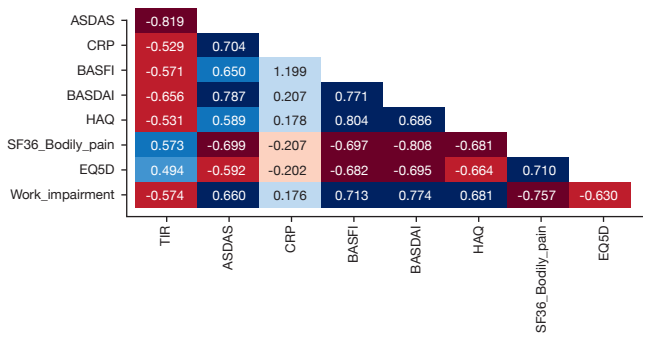
```
.by ID:gen percent_TIR_since_last_visit=1 if ASDAS<1.3 & ASDAS[_n-1]<1.3 & Visit!=1
.by ID:replace percent_TIR_since_last_visit = abs(ASDAS[_n-1]-1.3)/(abs(ASDAS-1.3)+abs(ASDAS[_n-1]-1.3)) if ASDAS>=1.3 & ASDAS[_n-1]<1.3 & Visit!=1
.by ID:replace percent_TIR_since_last_visit = abs(ASDAS-1.3)/(abs(ASDAS-1.3)+abs(ASDAS[_n-1]-1.3)) if ASDAS<1.3 & ASDAS[_n-1]>=1.3 & Visit!=1
.by ID:replace percent_TIR_since_last_visit = 0 if ASDAS>=1.3 & ASDAS[_n-1]>=1.3 & Visit!=1
```

Results

Following patients over time, TIR was significantly correlated ($p < 0.001$) with CRP (Spearman coefficient -0.529), BASFI (-0.571), BASDAI (-0.656), HAQ (-0.531), SF-36 bodily pain (0.573), EQ-5D utility (0.494) and WI (-0.574) (**Figure2**).

During the follow-up, TIR predicted EQ-5D utility in the test set (R^2=0.17; MSE=0.056) better than sustained remission (R^2=0.13; MSE=0.057) and somehow worse than point remission (R^2=0.19; MSE=0.053) (**Table 2**). Work impairment was also predicted by TIR more reliably (R^2=0.27; MSE=0.033) compared to sustained remission (R^2=0.20; MSE=0.035) and slightly less reliably than with point remission (R^2=0.28; MSE=0.031) (**Table 3**).

Figure 2.



Panel correlation matrix for parameters collected at up to 31 visits (up to 14 years on the first anti-TNF therapy). TIR is correlated with established measures of disease activity, disability and the health-related quality of life with all $p < 0.001$. As expected, the strongest correlations were observed with ASDAS-CRP and BASDAI.

The heatmap reflects the size of Spearman correlation coefficients. ASDAS: Ankylosing Spondylitis Disease Activity Score based on the CRP: C-reactive protein, BASFI: Bath Ankylosing Functional Index, BADAI: Bath Ankylosing Spondylitis. Disease Activity Index, HAQ: Health Assessment. Questionnaire, EQ5D: EuroQoL 5 Dimension questionnaire-derived utility, Work impairment was calculated from the WPAI: Work Productivity and Activity Impairment Questionnaire, SF-36: 36-Item Short Form Survey

Table 2. Prediction of the quality of life (EQ5D utility)

	TIR (0% to 100%)	Point remission	Sustained remission
Coefficient	0.183	0.158	0.137
p-value	< 0.001	< 0.001	< 0.001
Observations	5627	4963	4963
Clusters	1899	1826	1826
B/R R^2 Level 2	0.285	0.318	0.205
AIC	-1669	-1610	-1452
cross-validated R^2	0.172	0.190	0.128
cross-validated MSE	0.056	0.053	0.057

We used TIR, point remission and sustained remission to predict EQ-5D utility in a training sample via mixed effect clustered linear regression. Adjusted R^2 and mean squared error (MSE) of the prediction were calculated in the test set (split 70/30). B/R R^2: Bryk's & Raudenbush's coefficient of determination, AIC: Akaike information criterion

Table 3. Prediction of the work impairment (WPAI 0 to 100)

	TIR (0% to 100%)	Point remission	Sustained remission
Coefficient	-0.175	-0.155	-0.128
p-value	< 0.001	< 0.001	< 0.001
Observations	3835	3460	3460
Clusters	1456	1395	1395
B/R R^2 Level 2	0.381	0.389	0.286
AIC	-3223	-3050	-2851
cross-validated R^2	0.265	0.283	0.201
cross-validated MSE	0.033	0.031	0.035

We used TIR, point remission and sustained remission to predict WPAI work impairment in a training sample via mixed effect clustered linear regression. Adjusted R^2 and mean squared error (MSE) of the prediction were calculated in the test set (split 70/30). B/R R^2: Bryk's & Raudenbush's coefficient of determination, AIC: Akaike information criterion

Figure 5. QR Link to online calculator of the Time in remission (TIR) for physicians and patients

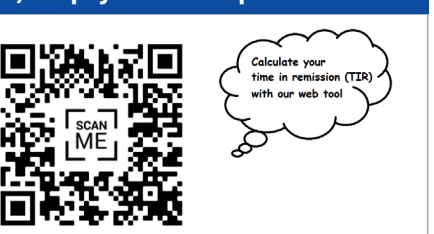


Figure 3.

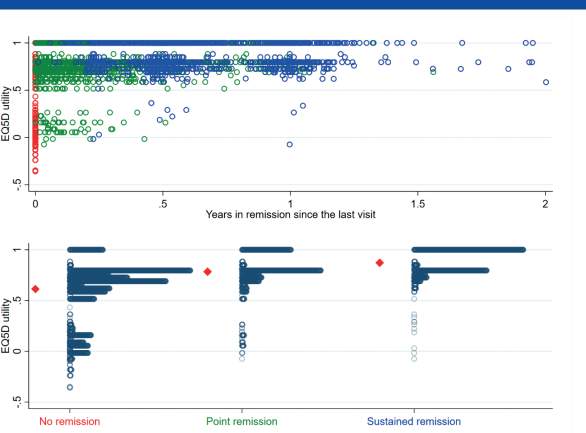


Figure 3 (upper): Scatter plot showing the two-way association between the years spent in remission (=TIR × follow-up) since the previous visit and the EQ5D utility. Patients with no remission, point remissions and sustained remissions are depicted in red, green and blue, respectively.

Figure 3 (lower): Dot plot showing the EQ5D utility in patients with no remission, point remission and sustained remission at the given visit. The red diamonds represent means.

Figure 4.

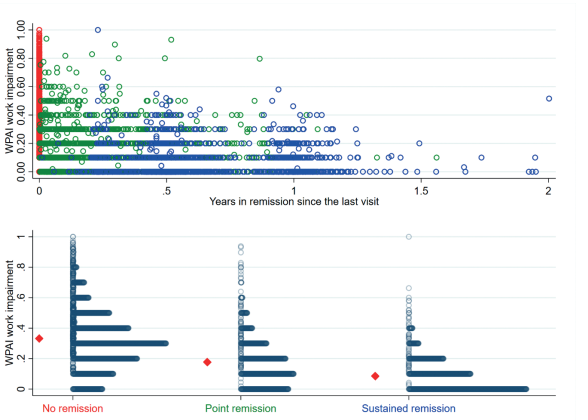


Figure 4 (upper): Scatter plot showing the two-way association between the years spent in remission (=TIR × follow-up) since the previous visit and the WPAI work impairment. Patients with no remission, point remissions and sustained remissions are depicted in red, green and blue, respectively.

Figure 4 (lower): Dot plot showing the WPAI work impairment in patients with no remission, point remission and sustained remission at the given visit. The red diamonds represent means.

Conclusion

- Time in remission (TIR) TIR represents an intuitive way of estimating unobserved true DA between scheduled visits in the form of a continuous variable.
- TIR estimated in ankylosing spondylitis patients during the years of anti-TNF therapy was correlated with established measures of disease activity, disability, quality of life and work impairment.
- TIR is an independent predictor of the quality of life and the work impairment, its performance seems comparable to established treatment targets, i.e. ASDAS-CRP point remission and sustained remission.
- In patients with ankylosing spondylitis, TIR can be used to describe their health state over time in a single number between 0 and 100 without losing information about achieving the treatment target.
- Years spent in remission can be calculated simply by multiplying TIR with the length of the follow-up.

References

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