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ORIGINAL ARTICLE

A proposal of simple calculation (ERI calculator) to predict the early response to TNF-α blockers therapy in rheumatoid arthritis

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Abstract Increasing evidence has been accumulated for treating rheumatoid arthritis (RA) with TNF-α blocking agents. The formulation and definition of an early indicator of patient's reactivity during therapy may be extremely simplified by a mathematical model of clinical response. We analyzed the most significant clinical and laboratory parameters of response of 35 homogeneous patients (30 women, 5 men mean age ± SD: 52.31 ± 12.30 years) treated with adalimumab 40 mg every 2 weeks associated with methotrexate (MTX) 10–15 mg/week and with a stable dosage of steroids for 30 weeks. The over time trend of the studied parameters showed a linear response, which has allowed the realization of a simple mathematical model. The formula derived from this mathematical model was then applied and therefore validated in a group of 121 patients previously treated with several anti-TNF-alpha agents for at least 6 months. We drafted a mathematical model (early response indicator, ERI) that, by using a simple calculation, allows us to identify a high percentage of responder patients after only 2 weeks of treatment. ERI identified a high percentage (88%) of patients responding after only 2 weeks, as was confirmed at weeks 30; the use of ERI calculation after 6 weeks increases the proportion of responding patients to 92% with a percentage of false negatives of only 12%. ERI could be a useful tool to early differentiate the responder from the non-responder patients.

Keywords Rheumatoid Arthritis · Mathematical model · TNF-alpha blocking agents

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Introduction

In the last few years, the extensive usage of antitumor necrosis factor-alpha (anti-TNF-α) agents in daily clinical settings has dramatically change the natural history of rheumatoid arthritis (RA) and has consequentially influenced the therapeutic algorithms for the disease [1–7]. Currently, the anti-TNF-α antagonists registered for RA include etanercept (Enbrel, Wyeth Europe Ltd, Maidenhead, UK), infliximab (Remicade, Centocor, Malvern, Pa, USA) and adalimumab (Humira, Abbott, Abbott Park, Illinois, USA): three different drugs that share the capacity of antagonize the inflammatory and harmful effects of TNF-α by preventing the binding of TNF-α to its natural receptor. Indeed, all these agents have demonstrated their sustained ability in improving disease symptoms, limiting progression of joint destruction and subsequently disability of RA patients [8–10]. Overall, literature data have reported that these anti-TNF-α agents are effective in 70% of RA patients and poorly efficacious in 30% of patients [11]. At the same time, it cannot be ignored that the use of anti-TNF-α agents is relatively expensive and not free from potential side effects [12]. Moreover, new biologic agents are emerging and have been approved for the therapy of

RA patients refractory or intolerant to TNF-alpha agents [13, 14]. Therefore, the early identification of patients responder and non-responder to anti-TNF-α agents would lead to many advantages in terms of time, safety and socioeconomic costs. Actually, among patients responder to anti-TNF-α agents clinical response can be complete or incomplete. The direct proportionality between the pharmacological effects and the clinical response in patients treated with anti-TNF-alpha agents leads us to analyze the clinical data by means of a mathematical model (indicator of reactivity) with the purpose of identify patients with a complete response to anti-TNF-α.

Mathematical models have been extensively and successfully used in different medical field to predict clinical response to different drugs [15–18].

Our aim was to create an early response indicator (ERI) that can predict the clinical response to TNF-α-blockers [9, 10] by means of a mathematical model. In this way, we will be able to distinguish between responder and non-responder patients, by means of a particular analysis based on the values of a clinical index and on the comparison of the temporal trend of clinical and biochemical values. In this context, the individual variability parameter, which can be modeled and quantified, will be also taken into consideration.

Patients and methods

This study was articulated in three different phases. In the first preliminary phase, we evaluated the mathematical behavior of the clinical and laboratory response to TNF-α-blockers in a limited cohort of RA patients. This step allowed us to elaborate the mathematical model that was subsequently utilized by a simple calculation to identify the clinical response in a different larger cohort of RA patients previously treated with anti-TNF-alpha agents. Finally, the mathematical model was externally validated by the comparison with the EULAR criteria for clinical response at 30 weeks.

In the first part of the study, 35 patients (30 women, 5 men, mean age ± SD: 52.31 ± 12.30 years, duration of disease: 98.66 ± 88.35 months), all fulfilling the ACR diagnostic criteria for RA [19], have been enroled and treated with adalimumab 40 mg every 2 weeks. Methotrexate (MTX) 10–15 mg/week and a stable dosage of steroids were allowed as concomitant medication. NSAIDs were allowed during the study as well. The following clinical and ematochemical parameters have been recorded during each visit (Table 1): number of tender joints (TJ), number of swollen joints (SWJ), erythrosedimentation rate (ESR), C-reactive protein (CRP) and clinical indexes of disease activity and pain registered by adopting a visual analogic scale (VAS 0–100) filled separately by both the physician and the patient. The observer-physician was always the same during the evaluation of the parameters. This first part of the study was conducted at the Rheumatology Unit of Pisa.

Table 1 Time of visit (weeks)

Visit	Weeks
V1	Baseline
V2	2
V3	6
V4	14
V5	22
V6	30

In this phase, we observed that the clinical response could be characterized by three different shapes: a complete response was distinguished by a linear curve, while, on the other hand, an incomplete or partial response and the condition of no responder were featured by a nonlinear curve.

The definition of clinical response was made on empirical grounds by including among responders all patients who, after 30 weeks (V6) of therapy, exhibit an indicator value that was within the normal range, or at least showed a reduction greater than 50% of the deviation from normality (see Table 2).

Once assumed, as our working hypothesis, that a complete response to therapy, when present, should take the approximate form of a linear curve, we elaborated a mathematical model, which can predict this clinical response (ERI). When some indicators, measured at time t, show a deviation $X(t)$ from its non-pathological value, linear response implies that, after a short lapse of time Δt, a positive response to therapy would lead to a reduction $\Delta X = X(t) - X(t + \Delta t)$ of the deviation from normality, and this reduction should be proportional to the time delay Δt, but especially to the deviation $X(t)$.

As a consequence, the relationship $\Delta X(t) = C^*X(t)^*\Delta t$ should (approximately) hold, where C is some (positive) constant coefficient, related to the specific indicator and only slightly dependent on the individual patient. A direct

Table 2 Standards for responders

Parameters	After 6 months
TJ	≥50% reduction
SWJ	≥50% reduction
ESR	≤0–30 mm/h
CRP	≤0–4 mg/dl
Illness activity VAS (Physician's)	≥50% reduction
Pain VAS	≥50% reduction
Illness activity (Patient's)	≥50% reduction

interpretation of C is obtained by noticing that, considering a time delay $\Delta t = 1/C$, we would obtain $\Delta X = X$, and therefore $1/C$ is a typical healing time.

Interpreting the above relationship as a finite difference equation, we can write down its solution in the form $X(t) = X(0)*B^t$, where $X(0)$ is the initial deviation from normality and the constant B (always less than 1) is related to C by the identity $C = -\ln B$. Therefore, the healing process should be indicated by an exponentially fast approach to normality. Notice that smaller values of B correspond to larger values of C, that is to faster healing.

In order to evaluate the approach to normality at time t, it was convenient to define the reduced value $R(t)$ of each indicator $I(t)$.

$$\mathrm{R}(t) = (I(t) - \mathrm{IN})/(I(0) - \mathrm{IN})$$

where $I(0)$ was the (typically anomalous) initial value of the indicator and IN was the average of acceptable values. For most indicators, IN was 0, with the exception of ESR whose IN was 15 and CRP whose IN was 2. When IN is different from zero, $R(t)$ might assume negative values, in which case its value must simply be replaced by zero.

Only indicators showing a significant number of responders and a nontrivial time dependence were taken into account. For this reason, we have finally excluded the indicator CRP from our analysis, since, in the case of CRP, the approach to normality was either absent or too fast to be significant.

The average of the reduced values $R(t)$ must be computed, for each sampling time t, in the group of responders. The resulting average values must be fitted by the parametrization

$$R(t) = A + (1 - A) * B^t.$$

We introduced the parameter A (predicted asymptotic average value of the indicator), which according to our above considerations, should be a number near 0.25, because we decided to accept as responders all patients whose final value of R was less than 0.50.

The analysis was substantially simplified if the fitted values of B for different indicators were not very different from each other. This would not be unexpected, because parameter B was related to the speed of reduction of the pathology, and therefore, the approach to normality should be approximately the same for all significant indicators. Another simplification may occur if the standard deviation of value distributions, which we denote by $V(t)$, had comparable values for the different indicators.

Under our simplifying assumptions (which must be empirically verified), we proposed a very simple definition of a general indicator at time t, obtained by taking the arithmetical average of the values of all (significant) reduced indicators. By taking the averages of the best fit parameters A, B and V, we could therefore define the values AM, BM and VM.

The standard condition for identifying responders at time t could at this point be expressed as follows: for any given patient, we computed the individual average of $R(t)$ on all selected indicators, and we assumed the patient to be a responder if the computed average satisfied the condition

$$R(t) < \mathrm{AM} + (1 - \mathrm{AM}) * \mathrm{BM}^t + 05 * \mathrm{VM}(t).$$

We were thus requiring that the residual pathology be less than the theoretical average predicted by the exponential (linear response) model, increased by half the average variation around the mean. Such an increase may seem to be very conservative, but this request was dictated by the need to exclude from the selection of a sufficient number of false responders.

The mathematical model (ERI) elaborated is reported below:

$$\mathrm{R}[np](t) = \frac{I\_[np](t) - \mathrm{lN}[n]}{I\_\{np\}(0) - \mathrm{IN}\_\{n\}}$$

If

$$\frac{\mathrm{R}[np](t)}{\text{number of parameter}} \leq 0.84 \text{ the patient is responder}$$

$\mathrm{I}\_[np](t) =$ value of parameter after 2 weeks

$\mathrm{lN}[n] =$ normal value

$I\_\{np\}(0) =$ value of parameter at time 0.

In the second part of the study, ERI index was tested on a group of 121 RA patients enroled at the Rheumatology Division of the University of Pavia (97 women, 24 men, mean age 56.84 ± 13.02 years, duration of disease 105.18 ± 88.35 months). These patients was previously treated with all the three anti-TNF-alpha agents registered for RA (adalimumab, infliximab and etanercept) according to the specific protocols approved for each single drug (Table 3) and regularly evaluated according to the visit time scheduled in Table 1.

For third step, we compared the ERI response with EULAR response at week 30th.

As suggested by the EULAR criteria, we considered indicative of a clinical response a ΔDAS28 > 1.2 (DAS28 V6-DAS 28V1), [12, 13]. Moreover, we assumed a DAS28 < 2.6 as indicator of clinical remission at week 30 [14].

Table 3 Characteristics of Pavia patients

Anti-TNF-alpha	Nr patients	Sex	Age (mean ± SD)
Adalimumab	44	37 ♀, 7 ♂	52.00 ± 14.55
Infliximab	59	44 ♀, 15 ♂	59.25 ± 11.05
Etanercept	18	16 ♀, 2 ♂	62.00 ± 12.23

Results

All the main quantities defined in the previous subsection (AM, BM, VM) have been evaluated on the 35 patients enroled in the first part of the study. The obtained values are reported in a more detailed way in "Appendix 1".

The obtained results, (see Table 10 and 11 Appendix 1) at various times, have allowed the identification of the asymptotic values of clinical response Table 4.

Moreover, by using the EULAR criteria as gold standard in the external validation, we identified 100 responders out of 121 patients at week 30 (visit 6). The ERI analysis permitted the identification of 104 responder patients after only 2 weeks (Table 5). In this analysis by adopting ERI index, we therefore observed 12 false negatives and 16 false positives after 2 weeks (Table 6). When tested at week 6, ERI allowed to recognize as responders the 92% of patients (Table 7). Description of false-positive patients and false-negative patients was reported in Tables 8 and 9.

Discussion

The availability of biologic drugs for RA therapy has underlined the importance of a prompt identification of responder from non-responder patients to this particular drugs. In this study, we verified that the mathematical modelization might help in the early identification of sustained responder patients. The novelty of the ERI is that this is not an index and it is not conceived to replace or to duplicate EULAR or ACR indexes in the assessing of RA activity or global clinical response. ERI is a simple formula that early detection of rheumatoid patients will be anti-TNF-alpha responders. ERI is able to predict the responders to anti-TNF-α therapy within the first 2 weeks of treatment, with the claim to faster and better individuate responder RA patients. Our assumption in constructing this mathematical modelling had been essentially that the sustained responders should have a linear clinical response to TNF-α blockers. Moreover, the variables that have to be calculated in the index should be easily collected and belong to the daily clinical armamentary of any rheumatologist. This model is essentially based on the mean of relative change of a limited number of variables also taking into account normal values of the variables. Many of the variables included in the analysis are part of the commonly adopted indices used in the evaluation of RA patients (i.e. tender and swollen joints, ESR illness activity). The ERI in addition took into account the VAS of pain and the VAS of illness activity as scored by the physician. The choice of calculate ERI using the ESR values rather than CRP is debatable, as CRP response to treatment is faster then ESR response and more sensitive to short-term changes. Nonetheless, considering the fast response of CRP to variations in disease activity, we considered that CRP would have been more useful for clinical trials rather than in daily clinical practice [20]. On the other hand, ESR would probably be better in daily clinical settings due to its slower response to variations in disease activity. In this study, we could, moreover, demonstrated that when included as the seventh variable CRP did not significantly modify the sensibility and the specificity of the ERI (see "Appendix 1"). In this study, ERI identified at 2 weeks a high percentage of responders for adalimumab (95%), infliximab (85%) and etanercept (80%) with an average of 88%. Therefore, it has demonstrated to be applicable to all the different anti-TNF-α agents, independently from their pharmacokinetics and specific mechanism of action.

The two most important advantages of the ERI are reconducible both to the small number of variables used and to the early identification of patients responders. This ERI calculation could be therefore easily and quickly applied at every visit, using the appropriate conversion factors leading to earlier start of an alternative treatment in non-responder patients. From this of view, our results have demonstrated that at week 6, the sensibility of the ERI increases from 88 to 92%.

We observed with particular attention the false-negative and the false-positive patients. The outpatients were treated

Table 4 Cut-off values of ERI after 2, 4, 6 and 8 weeks of treatment

Weeks	2	4	6	8
Patients responder if ERI values ≤	0,84	0,67	0,56	0,50

If the value extrapolated by the clinical parameter of the patient is lower than the cut-off index, the patient is responder

Table 5 The ERI analysis of 121 patients after 2 weeks compared to EULAR criteria of clinical response and remission

	Nr. patients	Responder ERI after 2 weeks	Responder Eular at 30 week	Remission Eular at 30 week	N of patients responder both according to ERI at 2 weeks and EULAR at 30 weeks
ADALIMUBAB	44	40	38	10	36
INFLIXIMAB	59	49	47	12	40
ETANERCEPT	18	15	15	7	12
TOTAL	121	104	100	29	88

Table 6 False-positive and false-negative patients analyzed by ERI and EULAR

	Number of false positive at 2 weeks with ERI	Number of false negative at 2 weeks with ERI	Number of false positive at 6 weeks with ERI	Number of false negative at 6 weeks with ERI
ADALIMUBAB	4	2	3	2
INFLIXIMAB	9	7	6	3
ETANERCEPT	3	3	2	3
TOTAL	16	12	11	8

Table 7 The ERI analysis of 121 after 6 weeks compared to EULAR criteria of clinical response and remission

	Nr. patients	Responder ERI after 6 weeks	Responder Eular at week 30	Remission Eular at week 30	N of patients responder both according to ERI at 6 weeks and EULAR at 30 weeks
ADALIMUBAB	44	39	38	10	36
INFLIXIMAB	59	50	47	12	44
ETANERCEPT	18	14	15	7	12
TOTAL	121	103	100	29	92

Table 8 Description of false-positive patients (14F, 3 M; age: 57.12 ± 14.33 mean ± SD; disease duration: 80.47 ± 67.09, months ± SD)

Group	Therapeutic modification
1. Adalimumab	At week 22, reduction of MTX
2. Adalimumab	No therapeutic modification
3. Adalimumab	No therapeutic modification*
4. Adalimumab	Low compliance for comorbidity with panic disorder
5. Infliximab	At visit 3, reduction of corticosteroids with worsening of symptoms*
6. Infliximab	Low compliance because of the onset of depression*
7. Infliximab	Owing to increasing levels of creatinine the patient has stopped NSAID and tramadol, taking only acetaminophen since week 22*
8. Infliximab	After visit 3, increased infliximab dosage*
9. Infliximab	After infusion 2 reduction of NSAID
10. Infliximab	At week 14, increased diclofenac, at week 54, onset of colon cancer.
11. Infliximab	Co-morbidity with fibromyalgia, after 2-week reduction of corticosteroid
12. Infliximab	Reduction of corticosteroid after visit 3
13. Infliximab	Reduction of NSAID and low compliance for recidivant urinary infection
14. Etanercept	Low compliance and drop out at week 30
15. Etanercept	At visit 2, reduction of corticosteroid and at visit 22, suspension of etanercept for suspected neuropathy*
16. Etanercept	Reduction of cortisone and low compliance for cerebral ischemia at week 22

* The patient was individualized as non-responder at week 6

with conventional therapies in concomitance with biological drugs. We observed a change in the concomitant therapies in false-negative patients, which could have modified the therapeutic response. Our formula shows the therapeutic response exactly at the point when a therapeutic alteration has been made. It is more difficult to explain the condition of the false-positive patients because these subjects showed a therapeutic response according to the ERI calculator but not according to the EULAR criteria (after 6 months). By analyzing our patients' cohort, we observed concomitant events (i.e. adverse events related to therapy, concomitant treatment suspension, etc.) during the treatment period which worsened the patients' health assessment. The limitation of this work is that, although ERI calculator is easy to employ, the mathematical procedure is complicated and difficult to understand for the rheumatologist.

Therefore, ERI was applied only to rheumatoid arthritis and should be interesting also in other diseases such as spondylarthritis. Parameters studied were chosen empirically and based on clinical experience and according to ACR and EULAR evaluations. The formula follows the rule of all or nothing, and nothing has been

Table 9 Description of false-negative patients (11F, 1 M; age: 56.83 ± 12.55 mean ± SD; disease duration: 80.42 ± 66.25, months ± SD)

Group	Therapeutic modification
1. Adalimumab	No therapeutic modification, patient treated with amitryptilina
2. Adalimumab	No therapeutic modification, intake of antihistaminic drugs at week 2 and at week 22, ciprofloxacin therapy
3. Infliximab	Increased corticosteroid after III infusion
4. Infliximab	No therapeutic modification after infusion 4 increased dosage of NSAID
5. Infliximab	At visit 3, arthrocentesis and steroid pre-treatment
6. Infliximab	Erythrosine intake at week 5 for a chronic parodontopatie and steroid reduction
7. Infliximab	No therapeutic modification*
8. Infliximab	After infusion 3, treatment with antibiotic therapy because of the onset of pulmonary disease*
9. Infliximab	After visit 3, preinfusion premedication with cortisonic drugs*
10. Etanercept	After visit 3, increased steroids dosage*
11. Etanercept	Appearance of dementia
12. Etanercept	At week 6, the patient stopped cyclosporine (CSA)

* The patient was individualized as responder at week 6

Table 10 Average values of reduced indicators at every time (weeks) evaluated in responders (35 patients enroled in the first part of the study)

	T0 = 0	T1 = 2	T2 = 6	T3 = 12	T5 = 20	T6 = 30	A	B
TJ	1	0.67	0.41	0.50	0.35	0.16	0.30	0.77
SWJ	1	0.61	0.53	0.37	0.22	0.15	0.20	0.83
ESR	1	0.62	0.43	0.25	0.08	0.10	0.11	0.82
VAS patients	1	0.62	0.55	0.42	0.43	0.25	0.37	0.73
VAS physician	1	0.64	0.55	0.54	0.39	0.29	0.40	0.74
Illness activity	1	0.62	0.55	0.49	0.40	0.26	0.37	0.73
Average	1	0.63	0.50	0.43	0.31	0.20	0.29	0.77

T week, *A* predicted asymptotic average value of the indicator, *B* corresponds to the typical factor by which the pathology is reduced (in responding patients) after each week of therapy

Table 11 Average values of variation ranges

	T1 = 2	T2 = 6	T3 = 12	T5 = 20	T6 = 30	Average
TJ	0.22	0.22	0.28	0.29	0.16	0.23
SWJ	0.26	0.27	0.32	0.22	0.19	0.25
ESR	0.32	0.35	0.41	0.27	0.29	0.33
VAS patients	0.23	0.27	0.26	0.29	0.13	0.24
VAS physician	0.21	0.21	0.22	0.24	0.23	0.22
Illness activity	0.24	0.28	0.23	0.33	0.16	0.25
Average	0.25	0.27	0.29	0.27	0.19	0.25

validated up to 6 months. It might be interesting to design tables for assessing ERI together with specific markers of disease as the title of anticitrullinated Ab or rheumatoid factors.

In conclusion, our "ERI calculator" might be a new tool for rheumatologists to faster and better individuate early responder RA patients treated with TNF-α blockers. "Appendix 2" showed how to use ERI and an example of its application.

Conflict of interest All author declare that they have no conflict of interest must.

Appendix 1

Results are presented in Tables 10 and 11, recalling that the temporal scale is 1 week, and therefore, the values of B correspond to the typical factor by which the disease process is reduced (in responding patients) after each week of therapy.

Based on the above-mentioned analysis, we elaborated the ERI mathematical model considering that:

1. The average values of the reduced indicators at time t were really very close, and we could therefore replace individual indicators with their average, thus simplifying

Table 12 Exponential fit of the average of indicators, optimized by the values AM = 0.29 and BM = 0.77

Weeks	2	4	6	8
RM(t)	0.71	0.54	0.44	0.38
RM + 0.5*VM	0.84	0.67	0.56	0.50

The values of RM(t) = AM + (1−AM)*BM(t) correspond to these values and have been computed in 2-week intervals

the model by considering exclusively the mean of relative change and taking into account normal values of the variables

2. The exponential fit of the average of indicators was optimized by the values AM = 0.29 and BM = 0.77. The values of RM(t) = AM + (1−AM)*BM(t) corresponding to these values and computed in 2-week intervals are reported in Table 12.
3. The values of variation ranges were basically constant in time and independent of the specific indicator. They could therefore be replaced by their general average, setting VM(t) = 0.25.
4. We can now define a function RM + 0.5 VM (Table 12), representing the value of the reduced indicator that a given patient must not exceed in order to be included among the responders.
5. The above procedure may be applied more than once, starting from a group of responders that have been selected after a very short time, but not very accurately, and improving the selection by a second check performed after a reasonable time (at least as long as the first reference interval).
6. In practice, our proposal was equal to accepting as responders all patients whose average entity of disease process, measured through the average of reduced indicators on a monthly basis, was smaller than 2/3 of its initial value 1 month after the beginning of therapy and smaller than half its initial value after 2 months. Tests may obviously be performed also at intermediate times, if desired.

Appendix 2: how to use ERI

$$\mathrm{R}[np](t) = \frac{I\_[np](t) - \mathrm{lN}[n]}{I\_\{np\}(0) - \mathrm{IN}\_\{n\}}$$

If

$$\frac{\mathrm{R}[np](t)}{\text{number of parameter}} \leq 0.84 \text{ the patient is responder}$$

I_[np](t) = value of parameter after 2 weeks,

lN[n] = normal value

$I\_\{np\}(0)$ = value of parameter at time 0

Example

	T0 = 0	T1 = 2 week	T6 = 30 week	Normal range
TJ	27	14	6	
SWJ	16	22	16	
ESR	62	73	75	0–30 mm/h
CRP	57.2	10.8	6	0–5 mg/dl
VAS patients	82	60	52	
VAS physician	78	64	55	
Illness activity	80	60	42	

$$\mathrm{ERI} = \frac{\frac{(14-0)}{(27-0)} + \frac{(22-0)}{(16-0)} + \frac{(73-15)}{(62-15)} + \frac{(10.8-2.5)}{(57.2-2.5)} + \frac{(60-0)}{(82-0)} + \frac{(64-0)}{(78-0)} + \frac{(60-0)}{(80-0)}}{7} = 0.79$$

TJ SWJ ESR CRP VAS patients VAS physician illness activity

The patients may be considered responder because when the value of ERI is ≤ 0.84.

$$\mathrm{ERI} = \frac{\frac{(14-0)}{(27-0)} + \frac{(22-0)}{(16-0)} + \frac{(73-15)}{(62-15)} + \frac{(60-0)}{(82-0)} + \frac{(64-0)}{(78-0)} + \frac{(60-0)}{(80-0)}}{7} = 0.77$$

TJ SWJ ESR VAS patients VAS physician illness activity

At week 30 the patient is responder also accordingly with EULAR criteria (ΔDAS28 = 1.96)

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