Haptoglobin blood assay to assess treatment compliance in rheumatoid arthritis patients treated with tocilizumab

Sirs,

It is currently difficult to guarantee that patients with rheumatoid arthritis (RA) take their treatment correctly. Several studies reported a medication nonadherence in RA patients (1-5). There are no simple biological assays to assess treatment compliance. Measuring drug levels is expensive and difficult to implement in routine care.

A decrease in haptoglobin (HP) levels has been described in a RA patient treated with tocilizumab (TCZ), an effective RA disease-modifying anti-rheumatic drug (6). Based on this case, we retrospectively measured the variation in HP levels in a sample of RA patients treated with subcutaneous (SC) or intravenous (IV) TCZ to determine whether a decrease in HP could be a relevant marker of compliance during RA treatment with TCZ.

RA patients participating in the RCVRIC cohort (PHRC No. ID-RCB-A01847-40), treated with TCZ and having had at least one HP dosage were included. They were the "RA-TCZ group". These same 25 patients were their own controls in the "RA-nonTCZ group" because they also received a biotherapy other than TCZ during the RCVRIC follow-up. We collected demographic characteristics, RA activity and biological parameters (HP, CRP), ideally before and after initiation of biotherapies (after 6 months if the data were available, otherwise after 3 or 12 months). We distinguished patients with low HP (level <0.3 g/l) and those with reduced HP (decrease in the HP level under treatment compared to the baseline value).

In the RA-TCZ group (n=25), HP was significantly lower under treatment compared to the baseline level (0.81±1.04 *vs*. 1.88±1.04 g/l; $p<0.001$), while the reduction was not significant in the RA-nonTCZ group (1.72±0.82 *vs*. 1.94±1.03; $p=0.06$). In both groups, the decrease in HP was correlated with the decrease in CRP ($r^2=0.84$; $p<0.001$ in the TCZ group and $r^2=0.47$; $p=0.03$ in the nonTCZ group). The decrease in HP was correlated with an increase in haemoglobin level only in the TCZ group ($r^2=-0.55$; $p=0.006$).

Ninety-one per cent of patients (22/24) had a reduction in HP under TCZ compared to 46.7% (14/21) under another biotherapy ($p=0.04$). Sensitivity and specificity of HP reduction for patients being treated by TCZ was respectivity 91% and 33%. Six patients (24%) had low HP under treatment in the RA-TCZ group, compared to no patients in the RA-nonTCZ group ($p=0.01$). Of the 4 RA patients treated with TCZ IV, 3 had a reduced HP (75.0%), while of the 20 treated with TCZ SC, 19 had a reduction in the HP rate (95%).

Of the 15 RA patients who had no systemic inflammation (CRP <5mg/l) at baseline when TCZ was initiated (15/25; 60%), 13 had a decrease of HP level, including 5 with a low HP under treatment.

We observed a greater frequency of reduction in HP level under TCZ SC compared to TCZ IV. This result could be explained by a greater variation in the HP level during IV administration of TCZ, and confirms the interest in monitoring the HP results in RA patients treated with TCZ SC to assess their compliance with the treatment.

The simple measurement of serum haptoglobin seems to be interesting and relevant for assessing compliance with subcutaneous TCZ treatment, especially in the case of a normal CRP level at TCZ initiation. Serum drug levels of TNFi and TCZ would be a more accurate biomarker for compliance, but these measures are not in routine care in all countries and their cost remains higher than the serum HP measurement.

These results need to be confirmed in larger cohorts of patients treated by TCZ, but no change in the haptoglobin level compared to the before-treatment level nor decrease under TCZ treatment seems to suggest unsatisfactory treatment compliance.

Table I. Comparison of tocilizumab and other biotherapies RA patients.

Parameters	Tocilizumab RA patients n=25			Other biotherapies RA patients n=25		
	Before treatment	Under treatment	*p*-value	Before treament	Under treatment	*p*-value
Age, years	55.7 ± 9.5			60.3 ± 11.5		
Women, %	21, 84%			21, 84%		
BMI	25.6 ± 4.9					
IV route, n, %	5, 20%			12, 48%		
DAS28	4.27 ± 1.14	3.04 ± 1.25	0.001	4.41 ± 1.09	3.76 ± 1.25	0.009
CDAI	19.0 ± 8.5	12.3 ± 9.8	0.01	22.9 ± 10.9	14.3 ± 8.7	0.001
CRP, mg/l	17.0 ± 26.4	5.7 ± 14.7	0.08	15.6 ± 19.2	11.3 ± 12.8	0.09
RBC, Giga/l	4.51 ± 0.38	4.61 ± 0.41	0.06	4.48 ± 0.47	4.61 ± 0.39	0.75
Haemoglobin, g/dl	13.2 ± 1.2	14.1 ± 1.0	<0.001	13.2 ± 1.6	13.6 ± 1.4	0.82
Haptoglobin, g/l	1.88 ± 1.04	0.81 ± 1.05	<0.001	1.94 ± 1.03	1.72 ± 0.82	0.16

RA: rheumatoid arthritis; BMI: Body Mass Index; IV: intravenous; DAS: Disease Activity Score; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index; RBC: red blood cell count. Values are mean ± standard deviation.

P.-Y. Montagnon
M. Beauger
M. Couderc, *MD*
A. Tournadre, *MD, PhD*
M. Soubrier, *MD, PhD*
S. Mathieu, *MD, PhD*

Rheumatology Department,
Gabriel Montpied Teaching Hospital,
Clermont-Ferrand, France.

Please address correspondence to:
Sylvain Mathieu
Rheumatology Department, Centre Hospitalier Universitaire Gabriel Montpied,
58 Rue Montalembert,
63003 Clermont-Ferrand, France.
E-mail: smathieu@chu-clermontferrand.fr

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References

1. ROSENBERG V, CHODICK G, XUE Z, FACCIN F, AMITAL H: Real-world data of adherence and drug survival of biologics in treatment-naïve and treatment-experienced adult patients with rheumatoid arthritis. *Adv Ther* 2023; 40: 4504-22. https://doi.org/10.1007/s12325-023-02607-w
2. NEYCHEVA S, NASEVA E, BATALOV Z, KARALILOVA R, BATALOV A: Adherence to biological therapies in patients with rheumatoid arthritis: a retrospective cohort study. *Rheumatol Int* 2023; 43: 1287-96. https://doi.org/10.1007/s00296-023-05327-0
3. GAUJOUX-VIALA C, BERGMANN JF, GOGUILLOT M *et al*.: Suboptimal management of rheumatoid arthritis in France: a real-world study based on data from the French National Health Data System. *RMD Open* 2023; 9: e003075. https://doi.org/10.1136/rmdopen-2023-003075
4. BERGMAN M, CHEN N, THIELEN R, ZUEGER P: One-year medication adherence and persistence in rheumatoid arthritis in clinical practice: a retrospective analysis of upadacitinib, adalimumab, baricitinib, and tofacitinib. *Adv Ther* 2023; 40: 4493-503. https://doi.org/10.1007/s12325-023-02619-6
5. PETRY L, ZUCKERMAN A, DECLERCQ J, CHOI L, LYNCH B, SAKNINI M: Primary medication nonadherence rates to specialty disease-modifying antirheumatic drugs for rheumatoid arthritis within a health system specialty pharmacy. *J Manag Care Spec Pharm* 2023; 29: 732-39. https://doi.org/10.18553/jmcp.2023.29.7.732
6. HERMANS MAW, van DAELE PLA: A puzzling haptoglobin level in a patient who is treated with tocilizumab. *Neth J Med* 2019; 77: 128.