Comparisons of hepatitis C viral replication in patients with rheumatoid arthritis receiving tocilizumab, abatacept and tofacitinib therapy

Despite recent advances in direct antiviral agents for hepatitis C virus (HCV), this infectious disease remains prevalent worldwide and presents a major therapeutic challenge in patients with rheumatoid arthritis (RA).[1] Our previous report demonstrated that use of antitumour necrosis factor (TNF)-α agents in patients with RA with HCV infection appears to be safe.[2] However, B-cell-targeted therapy with rituximab may lead to HCV viraemia by causing a decline in exosomal microRNAs.[3] Therefore, HCV viral replication may respond differently to biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) owing to the different mechanism of action in patients with RA.

Viral loads in HCV-infected patients with RA were reported to be unaffected during short-term therapy with tocilizumab, a monoclonal antibody targeting interleukin (IL)-6 receptor.[4 5] Abatacept, a fusion protein binding cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) that blocks the CD80/CD86 costimulatory pathways, has also been shown to be safe in patients with RA with HCV.[6] It remains unclear whether tofacitinib, a Janus kinase (JAK) inhibitor,[7] affects HCV viral activity in patients with RA. To study the impact of non-TNF-α bDMARDs and JAK inhibitors on HCV viral replication, we conducted a prospective study of patients with RA with concomitant HCV infection treated with tocilizumab, abatacept or tofacitinib.

In total, 32 patients who fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism criteria[8] for RA and HCV infection were enrolled (table 1). Twenty-three patients received non-TNF-α bDMARDs (tocilizumab, n=8; abatacept, n=15), while nine participants received tofacitinib therapy. Serum alanine aminotransferase (ALT) and HCV viral load were measured before and 1 year after treatment with bDMARDs and tsDMARDs. The majority of abatacept-treated patients with RA were biologics-naïve (93.3%) compared with their counterparts (tocilizumab, 75%; tofacitinib, 22.2%; p=0.001 by χ^2 test). None of the participants received direct antiviral therapy for HCV. There were no significant differences in serum ALT between baseline and 1 year after treatment with bDMARDs and tsDMARDs (figure 1; see online supplementary table S1). HCV viral loads before and after treatments are shown in figure 1. We found that HCV replications were significantly decreased in abatacept-treated patients with RA (p=0.015 by Wilcoxon signed-rank test). One patient exhibited an increase in ALT of Common Terminology Criteria for Adverse Events grade 1 severity after tocilizumab therapy. However viral loads before and 1 year after tocilizumab and tofacitinib treatment were comparable. Anti-IL-6 receptor and JAK inhibitors treatment did not appear to affect HCV viral activity.

This study is the first to demonstrate that T-cell costimulatory blocker therapy with abatacept might suppress HCV viral activity. Moreover, IL-6 blocker and JAK inhibitor did not interfere with HCV replication in patients with RA. These findings support the 2015 ACR guideline which states that the use of bDMARDs in patients with RA with HCV should not differ from those without HCV.[9] In addition, our results indicate that tofacitinib might not increase HCV viral replication, which could have important implications for treatment decision-making. Further study is necessary to clarify whether tsDMARDs with differential JAK family specificity are safe in patients with RA with HCV.

It is well known that the levels of transaminases in patients with HCV are not consistently correlated with viral replication. Our study demonstrated that the changes of ALT and HCV viral loads were similar before and after treatment with tocilizumab or tofacitinib (figure 1). Interestingly, we revealed significantly decreased HCV viral loads after abatacept treatment, consistent with a previous report that showed HCV RNA might become undetectable after costimulatory blockade.[6] Patients with RA may show different states of T-cell exhaustion, which could be restored after abatacept treatment, further enhancing T-cell functionality and suppressing viral replication.[10] Given that the number of abatacept-treated patients is limited, prospective long-term study is needed to recruit a larger number of patients with RA with concomitant HCV infection.

In conclusion, tocilizumab, abatacept and tofacitinib appear to be safe for treatment of patients with RA with HCV infection. Collaboration between rheumatologists and hepatologists is suggested in order to consider the suitability of direct antiviral therapy and to monitor viral loads in HCV-infected patients with RA.

Table 1 Demographic data and concomitant medication of patients with rheumatoid arthritis and hepatitis C receiving tocilizumab, abatacept and tofacitinib therapy

	Tocilizumab (n=8)	Abatacept (n=15)	Tofacitinib (n=9)	P value
Age	70.0 (65.0–71.8)	65.0 (54.0–72.0)	64.0 (59.5–70.0)	0.480
Gender				0.881
Female	7 (87.5%)	14 (93.3%)	8 (88.9%)	
Male	1 (12.5%)	1 (6.7%)	1 (11.1%)	
Disease duration, years	12.0 (7.5–13.0)	12.0 (5.0–13.0)	12.0 (9.5–22.5)	0.229
RF-positive	8 (100.0%)	13 (86.7%)	8 (88.9%)	0.567
ACPA-positive	8 (100.0%)	12 (80.0%)	7 (77.8%)	0.369
Biologics-naive	6 (75.0%)	14 (93.3%)	2 (22.2%)	0.001**†
DAS28	5.9 (5.3–6.5)	6.4 (6.0–6.9)	5.6 (4.6–6.7)	0.088
ESR (mm/hour)	51.5 (40.3–69.8)	41.0 (31.0–65.0)	34.0 (23.0–84.0)	0.460
CRP (mg/dL)	2.8 (1.1–4.9)	0.5 (0.3–1.4)	1.2 (0.1–2.2)	0.145
Daily glucocorticoids dose (mg)	5.0 (3.1–9.4)	7.5 (5.0–10.0)	5.0 (1.3–10.0)	0.385
Methotrexate	1 (12.5%)	8 (53.3%)	2 (22.2%)	0.097
Salazopyrin	1 (12.5%)	5 (33.3%)	2 (22.2%)	0.533
Hydroxychloroquine	5 (62.5%)	10 (66.7%)	4 (44.4%)	0.550
Leflunomide	4 (50.0%)	4 (26.7%)	2 (22.2%)	0.407
Ciclosporin	1 (12.5%)	3 (20.0%)	1 (11.1%)	0.812

Data are expressed as median (IQR).
Comparisons by χ^2 test and Kruskal-Wallis test. **p<0.01
†Post-hoc analysis, abatacept vs tofacitinib, p=0.002.
ACPA, anticitrullinated protein antibody; CRP, C reactive protein; DAS28, 28-Joint Disease Activity Score; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Yi-Ming Chen,[1,2,3,4] Wen-Nan Huang,[1,3] Tsai-Ling Liao,[2,4] Jun-Pen Chen,[2] Sheng-Shun Yang,[3,5] Hsin-Hua Chen,[1,2,3,4] Tsu-Yi Hsieh,[1] Wei-Ting Hung,[1] Yi-Hsing Chen,[1,3] Der-Yuan Chen[6,7]

[1]Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan
[2]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan
[3]Faculty of Medicine, National Yang Ming University, Taipei, Taiwan

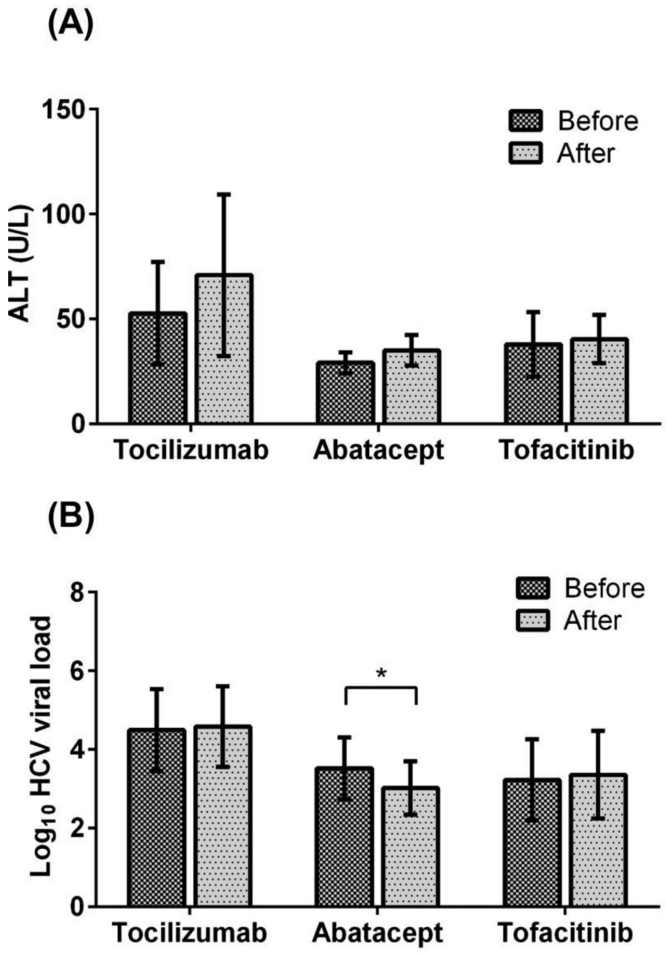

Figure 1 Comparisons of (A) serum alanine aminotransferase (ALT) and (B) hepatitis C virus (HCV) viral load before and after tocilizumab, abatacept and tofacitinib treatment. Data are mean±1 SEM. HCV viral loads were expressed as log10 of the detected values. *P=0.015 by Wilcoxon signed-rank test.

[4]Institute of Biomedical Science and Rong Hsing Research Center for Translational Medicine, National Chung Hsing University, Taichung, Taiwan
[5]Division of Gastroenterology and Hepatology, Taichung Veterans General Hospital, Taichung, Taiwan
[6]Rheumatology and Immunology Center, China Medical University Hospital, Taichung, Taiwan
[7]School of Medicine, China Medical University, Taichung, Taiwan

Correspondence to Professor Der-Yuan Chen, Rheumatology and Immunology Center, China Medical University Hospital, Taichung, 40447, Taiwan; dychen@vghtc.gov.tw and Dr Yi-Hsing Chen, Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung 40705, Taiwan; ysanne@vghtc.gov.tw

Handling editor Josef S Smolen

Acknowledgements The authors are grateful to the Biostatistics Task Force of Taichung Veterans General Hospital, Taiwan, for assistance with statistical analysis. The authors sincerely appreciate the assistance of the Center for Translational Medicine of Taichung Veterans General Hospital.

Contributors Y-MC and W-NH conceived and designed the study, conducted the data analysis, and drafted and revised the manuscript. J-PC performed the statistical analysis and revised the manuscript. T-LL, S-SY, H-HC, T-YH and W-TH acquired clinical data and revised the manuscript. D-YC and Y-HC generated the original hypothesis, conceived and designed the study, acquired clinical data, conducted the data analysis, and drafted and revised the manuscript.

Funding This study was supported by a grant from Taichung Veterans General Hospital, Taiwan (TCVGH-1077307C).

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-214400).

To cite Chen Y-M, Huang W-N, Liao T-L, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2018-214400

Received 5 September 2018
Revised 6 December 2018
Accepted 8 December 2018

Ann Rheum Dis 2019;**0**:1–2. doi:10.1136/annrheumdis-2018-214400

REFERENCES

1. Maillefert JF, Muller G, Falgarone G, *et al*. Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2002;61:635–7.
2. Chen YM, Chen HH, Chen YH, *et al*. A comparison of safety profiles of tumour necrosis factor α inhibitors and rituximab therapy in patients with rheumatoid arthritis and chronic hepatitis C. *Ann Rheum Dis* 2015;74:626–7.
3. Liao TL, Hsieh SL, Chen YM, *et al*. Rituximab may cause increased hepatitis C virus viremia in rheumatoid arthritis patients through declining exosomal MicroRNA-155. *Arthritis Rheumatol* 2018;70:1209–19.
4. Nagashima T, Maruyama A, Kamata Y, *et al*. Unchanged serum viral load and liver function during tocilizumab treatment in a patient with rheumatoid arthritis and hepatitis C virus infection. *Rheumatol Int* 2012;32:2231–2.
5. Dragonas C, Ehrenstein B, Fleck M. Tocilizumab treatment in a patient suffering from rheumatoid arthritis and concomitant chronic hepatitis C infection. *Rheumatology* 2012;51:1520–1.
6. Mahajan TD, Hooker R, Maher L, *et al*. Abatacept therapy for rheumatoid arthritis in the setting of hepatitis C infection. *J Clin Rheumatol* 2010;16:332–4.
7. Boor PPC, de Ruiter PE, Asmawidjaja PS, *et al*. JAK-inhibitor tofacitinib suppresses interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and antiviral effects of interferon alfa. *Transl Res* 2017;188:67–79.
8. Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
9. Singh JA, Saag KG, Bridges SL, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
10. Frenz T, Grabski E, Buschjäger D, *et al*. CD4(+) T cells in patients with chronic inflammatory rheumatic disorders show distinct levels of exhaustion. *J Allergy Clin Immunol* 2016;138:586–9.