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Brief report "Personalized cytokine-directed therapy with tocilizumab for refractory immune checkpoint inhibitor-related cholangiohepatitis"

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KEY WORDS

Immune-related adverse events, immune checkpoint inhibitor-related hepatitis, immune checkpoint inhibitor-related cholangitis, anti-IL-6 therapy

ABBREVIATIONS

IRCH	immune checkpoint inhibitor-related cholangiohepatitis
ICIs	Immune checkpoint inhibitors
irAE	Immune-related adverse event
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4

PD-(L)1	Anti-programmed-death-1/programmed-death-ligand-1
AIH	Autoimmune hepatitis
TCZ	Tocilizumab
CRP	C-reactive protein
CS	Corticosteroid
MMF	Mycophenolate mofetil
IL-1RA	Interleukin-1 receptor antagonists
IFN-α/β	Interferon-α/β
PDN	Prednisone
TNF-α	Tumor necrosis factor-α
IL	Interleukin
IL-1RA	Interleukin-1 receptor antagonist
IFN	Interferon
TNF	Tumor necrosis factor
CCL	C-C motif chemokine ligand
CXCL	C-X-C motif chemokine ligand
MCP-1	Monocyte chemoattractant protein-1
MP	Intravenous methylprednisolone
MIP	Macrophage inflammatory protein
KC	Keratinocyte chemoattractant
MIG	Monokine-induced by gamma interferon
SDF-1	Stromal cell-derived factor 1
BLC	B lymphocyte chemoattractant
NGF	Nerve growth factor
BDNF	Brain-derived neurotrophic factor
EGF	Epidermal growth factor
FGF-2	Fibroblast growth factor 2
HGF	Hepatocyte growth factor
LIF	Leukemia inhibitory factor
PDGF-BB	Platelet-derived growth factor-BB
PlGF-1	Placental growth factor-1
SCF	Stem cell factor
VEGF	Vascular endothelial growth factor
BAFF	B-cell activating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
G-CSF	Granulocyte colony-stimulating factor

ABSTRACT

Introduction. For patients with corticosteroid (CS)-refractory immune checkpoint inhibitor-related cholangiohepatitis (irCH), no consensus exists regarding treatment, and outcomes remain poor. We evaluated the possibility of personalized treatment according to the patient's cytokine profile and the immunohistopathologically assessment of the predominant immune infiltrate type of liver tissue.

Methods. NSCLCs with CS-refractory irCH were analyzed by immunohistochemistry (IHC) of liver biopsy, serum cytokine panel, and CyTOF assessment of PBMC immune cell monitoring.

Results. A total of three consecutives patients with irCH were identified. We found a predominant T-cell infiltrate and an IFN-γ/Th1 proinflammatory cytokine profile. Here, we report for the first time that a T-cell-targeted therapy with the IL-6 receptor-neutralizing antibody tocilizumab (TCZ), which inhibits signaling downstream of interferon-γ (IFN-γ) and several other JAK-dependent cytokines, is an effective single cytokine-directed therapy for CS-refractory irCH. Three patients with severe and CS-refractory irCH who were treated with TCZ showed persistent clinical and biological remission.

Conclusion. Dysregulation of the IL-6/T-cell axis may contribute to the pathogenesis of CS-refractory irCH. Our observations suggest that IL-6 blockade appears to show promise in the treatment of CS-refractory irCH. The results from our three patients need to be confirmed in a larger patient population.

INTRODUCTION

Immune-mediated hepatotoxicity associated with immune checkpoint inhibitors (ICIs) is a well-recognized potentially serious immune-related adverse event (irAE), with a wide clinical spectrum ranging from asymptomatic elevations in liver enzymes detected during routine monitoring, as seen in 25% of patients with grade 3-4 hepatitis[1], to acute liver failure, which is a major cause of death.[2-4] Fever, abdominal pain and jaundice in cases of cholestatic injury have also been described.[1] Few cases of fulminant hepatic failure have been reported.[4,5] Risk depends on the class of ICIs, dosage and eventual comedications.[1,6,7] Severe hepatitis (grade 3 and 4) has been reported in approximately 1 – 2.2% of patients treated with nivolumab or pembrolizumab monotherapy.[8,9]

First-line treatment with high doses of systemic corticosteroids (CSs) is usually recommended for persistent grade 2 and grade 3-4 liver injuries.[10,11] Unfortunately, limited data are available on the efficacy of second-line therapies. Currently, there are no specific therapeutic guidelines for CS-refractory irCH management, and the majority of patients are treated with various sequences of immunosuppressant drugs. This paucity of large-scale randomized controlled trials in this field makes the treatment of CS-refractory irCH very challenging.

Although the pathogenesis of irCH is not fully understood, we investigated the possibility of treating severe irCH according to the cytokine profile and on the basis of an immunohistopathologically guided strategy.[3] Given the presence of a predominant T-cell immune infiltrate on the immunohistopathological liver assessment and of the IFN-γ/TH1/IL-6-cytokine signature, blocking IL-6 signaling represents an attractive target.[12-14] IL-6 is an upstream pleotropic proinflammatory cytokine produced during the early stages of inflammation and plays a central role in driving the pathogenesis of autoimmune hepatitis[15], as well as in the proliferation, survival and activation of cytotoxic T cells.[16] Furthermore, the IL-17/IL-6 axis plays an important role in the pathogenesis of many liver diseases by regulating innate immunity, adaptive immunity, and autoimmunity.[15]

Here, we report, for the first time, three consecutive patients with severe irCH who received successful personalized treatment with the anti-IL6R antibody tocilizumab (TCZ) based on their cytokine profiles and on the liver biopsy predominant immune infiltrate, resulting in rapid clinical and biological remission. We performed molecular and cellular characterization of each patient's response by longitudinal profiling of the cytokine and chemokine serum levels using a 50-marker panel and analyzing liver biopsies.

METHODS

Clinical Data. We report three consecutive patients with non-small cell lung cancer who developed cholangiohepatitis while undergoing pembrolizumab treatment. The clinical and biological characteristics of the patients as well as the therapy regimens are summarized in Table 1.

RESULTS

Clinical course with tocilizumab treatment in CS-refractory irCH. The baseline Th1 cytokine profile showed high IL-6 levels (patient 1), and predominant T-cell infiltrate was

visible in the livers of the three patients (Figure 2). Thus, TCZ, an anti-IL6R antibody, was administered to all three patients, resulting in rapid improvement of their clinical status. Similarly, rapid improvements in liver function indicators including aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and bilirubin, as well as ferritin, were observed (Figure 1). Of note, the adjunction of TCZ allowed normalization of creatinine (patient 1) and hemoglobin (patient 2). Patients 1 and 2 required two doses of TCZ, whereas patient 3 required only one dose.

Serum cytokine signature associated with CS-refractory irCH. Despite the previous course of CS, withdrawn 10 days before performing the first cytokine panel, patient 1 exhibited high baseline levels of circulating proinflammatory cytokines, including IFN-γ and IFN-γ-induced chemokines (IL-6, IL-18, CXCL1, CXCL9, CXCL10, CXCL11, CXCL13 and G-CSF). We also observed elevated levels of anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist (IL-1RA). The level of TNF-α was not increased (Figure 2A). For patients 2 and 3, although the cytokine panel evaluation was performed six days after starting high-dose CS, which most likely affected the results, we observed an increase in pro-inflammatory cytokines including IFN-γ-induced chemokines (IL-18, IL-7, CXCL1, CXCL9, CXCL10 and CXCL13), as well as IL-10 anti-inflammatory cytokines (Table 1). After two administrations of TCZ, the levels of proinflammatory cytokines, especially IFN-γ- and IFN-γ-induced chemokines, were significantly decreased for patient 1 (Figure 2). As expected and reported previously, the serum level of IL-6 increased during TCZ treatment.[17]

Histologic and immunohistochemical testing. The diagnosis of cholangiohepatitis was supported by histopathological findings of the liver biopsies in the three patients. In patient 1, acute hepatitis with portal inflammation, interface hepatitis and lobular microgranulomatous inflammation was found together with focal cholangitis. Immunostaining revealed that inflammatory cells were mainly T lymphocytes, almost equally CD4+ and CD8+, and that plasma cells were exceptional (Figure 2B). Transjugular liver biopsy performed in patient 2 demonstrated a background of steatofibrosis related to previous known alcohol consumption, with a superimposed acute inflammatory process. Severe portal inflammation with interface hepatitis was associated with ductular reaction and biliary metaplasia of the periportal hepatocytes. Again, inflammation mainly comprised T lymphocytes, with CD4+ and CD8+ cells in almost equal proportions (Figure 2C). At approximately day 20, despite the repeated administration of high intravenous methylprednisolone (MP) over several days, the patient's

liver function tests and ferritin have not been significantly improved, requiring a high dose of MP. The liver biopsy was then repeated for patient 2 after two weeks. Histopathologic findings in the second biopsy were consistent with evolving immunotherapy-related cholangitis. The amount of inflammation had decreased, but the bile duct lesions were more important, associated with ductopenia, biliary infarcts and histological signs of chronic cholestasis (Figure 2C, second biopsy). Within the residual inflammatory infiltrate, T lymphocytes still predominated, and CD4+ and CD8+ cells were still equally represented. In patient 3, portal inflammation was again composed mainly of T lymphocytes, with CD4+ and CD8+ cells organized around the portal bile duct in a concentric way reminiscent of primary biliary cholangitis or primary sclerosing cholangitis, and infiltrating the epithelial lining of the duct (Figure 2D). There was also some interface and lobular hepatitis.

DISCUSSION

Poor outcomes have been reported in patients presenting with CS-refractory irCH. Little progress in the development of new treatments has been made in recent decades. Additional antiproliferative immunosuppressants are recommended in refractory cases. Given the paucity of data on second-line immunosuppressive therapy in irCH, recommendations are defined by analogy with autoimmune hepatitis, indicating mycophenolate mofetil and tacrolimus as potentially effective therapeutic agents.[11] Antithymocyte globulin has also been reported as an effective treatment.[18]

Given this lack of established therapies, we investigated the possibility of personalized treatment for CS-refractory irCH according to the patient's cytokine profile and to the immunohistopathologically personalized assessment of liver tissue. Targeted therapies aim to inhibit key proinflammatory proteins involved in the pathophysiological processes of irCH, allowing better efficiency and fewer potential side effects of the high immunosuppressive burden.

This pathogenic cytokine signature is characterized by strong IFN-γ/Th1 cell polarization (Figure 2A and table 1). Of note, our patients also showed elevated levels of anti-inflammatory regulatory cytokines such as IL-1RA and IL-10 (Figure 2A and table 1). Presumably, these antagonist pathways are induced to contain the inflammatory response by suppressing the hyperactivation of Th1 cell and monocyte/macrophage functions and to

protect the host from an excessive immune response. Interestingly, we found markedly increased serum levels of CXCL9 and CXCL10, chemokines induced by IFNγ. Increased levels of these CXCL3 ligands are apparent in primary biliary cirrhosis and autoimmune hepatitis. CXCL9 correlates with liver inflammation and fibrosis[19], whereas CXCL10 is known to be upregulated in patients affected by nonalcoholic steatohepatitis (NASH)[20]. These ligands activate the NF-κB pathway and pro-inflammatory cytokines such as TNF-α, IL-1β, and MCP-1[21], acting as a promoter of both innate and adaptative inflammatory responses. Further investigations are required to validate CXCL9 and CXCL10 as biological markers of liver inflammatory injury in irCH.

An interesting feature of CS-refractory irCH was the predominant T-cell infiltration composed equally of CD4+ and CD8+ cells on liver biopsy in the three patients, despite several days of high-dose CS (Figure 2). The second liver biopsy for patient 2 remained rich in T lymphocytes, suggesting a possible link between liver function degradation and the presence of T lymphocytes resistant to high doses of CS. Common histopathologic findings in irCH include panlobular hepatitis and isolated central zonal necrosis. In severe cases, pan- or multiacinar confluent necrosis can be observed.[7] Microabscesses and granulomatous or microgranulomatous lesions are also seen.[1,22] Portal inflammation targeting the bile duct with ductular reaction and cholangitis are characteristic of the *biliary pattern.*[22] Compared to histopathologic findings seen in autoimmune hepatitis (AIH), plasmacytosis, hepatocellular rosettes and confluent necrosis are less frequent in ICI-induced liver disease, while lobular hepatitis and portal inflammation are common to both entities.[7] Immunostaining typically demonstrates T-lymphocyte-predominant infiltrates. Infiltration of predominantly CD8+ lymphocytes is observed in patients receiving anti-CTLA-4, while CD8+ and CD4+ cells are equally represented in liver injury induced by anti-PD1/PD-L1.[1] The importance of CD8+ cell infiltration is also different from that in classical autoimmune hepatitis and cholangitis.[22]

Unfortunately, although the histopathologic assessment would be helpful to support the diagnosis, to evaluate the degree of tissue injury and to individualize the treatment strategy, liver biopsy is not routinely performed.

IL-6 is an upstream pleotropic proinflammatory cytokine that plays a central role in driving the pathogenesis of autoimmune hepatitis[15] along with the proliferation, survival and activation of cytotoxic T cells.[16] Furthermore, the IL-17/IL-6 axis plays an important role in

the pathogenesis of many liver diseases by regulating innate immunity, adaptive immunity, and autoimmunity.[15] Therefore, in contrast to blocking single cytokines further downstream, which might not have any impact on the activity of the various other cytokines propagating immune activation and end-organ damage, blocking the IL-6/IL-6R axis affects the production of multiple cytokines that contribute to liver injury. Patient 1 serum analysis revealed high levels of IL-6 and IL-18, which are proinflammatory cytokines, both reported to be involved in the pathogenesis of autoimmune hepatitis. Suppressing this pathological immune activation with the anti-IL-6R antibody TCZ seems to be a promising strategy for CS-refractory irCH, resulting in rapid resolution of symptoms and normalization of the pathological laboratory values.

Of note, IL-6 promotes the production of JAK-STAT–dependent cytokines (e.g., interferon-γ and Th1 cytokines), differentiation of IL-17-producing T helper cells (Th17), and proliferation and cytotoxic activation of CD8+ T cells while inhibiting the expression of regulatory T cells (Tregs).[23] The imbalance resulting from IL-6 hypersignaling potentially increases this inflammatory response initiated by activated T lymphocytes in patients developing irAEs as reported in supplementary figure 1 where, despite the use of MP for several days, PBMC T cells of patient 3 exhibited elevated levels of CD38 and HLA-DR markers which are characteristic of high level immune activation. Very interestingly, in contrast to MP, TCZ treatment allowed the normalization of T cell phenotypic profiles.

Most interestingly, it was reported that the increase in hepatic IL-6 expression contributes to the pathogenesis of AIH.[15] Furthermore, in patients receiving anti-PD(L)1, Treg depletion may result from inhibition of PD1-mediated enhancement of Foxp3.[24]

Additionally, the emerging role of IL□6 hypersignaling in the impairment of the immune response against tumors has been recognized. Dysfunction of innate and adaptive immunity mediated by IL-6 results in reduced activation and priming of tumor□specific T cells, decreased Th1 differentiation of CD4+ T cells, inhibited maturation of dendritic cells, and increased production of immune□suppressive factors such as IL□10, prostaglandin E2 (PGE 2), and vascular endothelial growth factor (VEGF).[25] Therefore, given their potential antitumorigenic properties, IL-6 blocking therapeutic agents, such as TCZ, represent an interesting option for the management of CS-refractory irAEs. Such an antitumor synergy

could be evoked in patients 1 and 2, whose cancers remained in partial remission despite the absence of oncological treatment for 7-8 months.

Although less frequently than other immunosuppressive drugs (ISs), such as mycophenolate mofetil or azathioprine, elevations in liver enzyme levels and extremely rare cases of severe drug-induced liver injury have been reported with TCZ, making TCZ a relatively safe IS.

Taken together, the data regarding the rapid and sustained clinical and biological response to TCZ treatment suggest that dysregulation of the IL-6/T-cell axis contributes to the pathogenesis of CS-refractory irCH. The results from our patients need to be confirmed in a larger patient population, yet our observations suggest that IL-6 blockade appears to show promise in the treatment of irCH. We point to the urgent need for additional studies to improve insights into the molecular and cellular mechanisms underlying irCH to draw more patient- and histological-tailored guidelines for management.

Figure legends

Table 1. Characteristics, clinical, biochemical data, and treatment regimen of the three patients. ANA, antinuclear antibody; AIH, autoimmune hepatitis; AIN, acute interstitial nephritis; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; irAEs, immune-related adverse events; CS, corticosteroid; TCZ, tocilizumab; PR, partial remission.

Figure 1. Assessment of clinical and biochemical remission of irCH with tocilizumab therapy. The three panels show biochemical data at diagnosis, during treatment and at discharge. Despite receiving high-dose MP boluses, the two patients had an immune flare associated with rapid increases in ferritin, AST, ALT, bilirubin, and creatinine levels and decreases in hemoglobin levels. Patients 1 and 2 received two doses of TCZ 8 mg/kg and patient 3 received only one dose. This allowed for the rapid decrease in liver function tests and ferritin levels and was associated with the rapid improvement in hemoglobin levels and clinical amelioration. The patients were then progressively weaned from CSs and did not experience any recurrence. NSAID, Nonsteroidal anti-inflammatory drug; IV, intravenous, CS; corticosteroid; TCZ, tocilizumab.

Figure 2. Assessment of cytokine signatures and histological characteristics. Panel A shows the results of the cytokine panel of PBMCs**.** Heat map of scaled pg/µl values. Columns (i.e., cytokines) are scaled to facilitate the comparison of the detected levels of the cytokines, which are color-coded from white to red (low to high levels of cytokines detected). The panel was obtained for patient 1 at diagnosis and repeated after TCZ treatment. Panels B-F show the results of histological features and immunohistochemical testing of liver biopsy specimens from patient 1 (B), patient 2 (C) and patient 3 (D). Figure 2B-Case 1. Portal inflammation with interface hepatitis and focal cholangitis (arrows). Inflammation was composed of T lymphocytes, with $CD4^+$ and $CD8^+$ cells almost equally represented. Figure 2C-case 2. First biopsy. Portal inflammation with interface hepatitis, ductular reaction and biliary metaplasia on cytokeratin 7 (K7) immunostaining. Inflammatory infiltrate was composed of T lymphocytes, with $CD4^+$ and $CD8^+$ cells almost equally represented. Figure 2C-case 2. Second biopsy. Bile duct alterations and vacuolization (arrows). Bile infarcts (arrow) and biliary metaplasia on K7 immunostaining together with ductopenia. Figure 2D-case 3. Inflammation is mainly organized around the bile duct in a concentric way better seen on K7 immunostaining. Inflammatory infiltrate is made of T lymphocytes, with both $CD4^+$ and $CD8^+$ cells.

Author contributions. MO conceived the study and the treatment, wrote the manuscript and prepared the figures and the table. LM wrote the manuscript and prepared the figures and table. MP performed the cytokine analysis and the heap map. CS performed the immunohistochemical assessment and analysis. HB, NM, TN, SP and JY participated in medical care. All authors commented on and revised the manuscript.

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Table 1. Patient's characteristics with clinical and biochemical data at diagnosis and during treatment

	Patient 1	**Patient 2**	**Patient 3**
Gender	Male	Male	Female
Age	83 years	67 years	70 years
Disease	Squamous cell carcinoma stage IIIB	Squamous cell carcinoma stage IIIB	Lung adenocarcinoma stage IVB
Cancer treatment	Carboplatin, vinorelbin, pembrolizumab (4 cycles)	Carboplatin, gemcitabine, pembrolizumab (4 cycles)	Pembrolizumab (1 cycle)
Additional work-up	AST 874 U/L (14-50) ALT 655 U/L (11-50) ALP 969 U/L (36-108) Gamma-GT 1736 U/L (10-71) Bilirubin 54 µmol/L (0-21) Ferritin 13095 µg/L (30-400) CRP 45 mg/L (<10) ESR >44 mm/h (<10) Infectious panel negative for: HAV, HBV, HCV, HEV, CMV, HIV 1/2, HSV 1/2, TB spot EBV DNA (quantitative PCR) whole blood : 4787 copies/ml EBV DNA (quantitative PCR) liver biopsy : negative Auto-immune panel negative for: Complement (C3c, C4), ANA and autoantibodies associated with autoimmune liver diseases (anti-smooth muscle, anti-actin, anti-M2, anti-gp210, anti-sp100, anti-LKM1, anti-LC1, anti-SLA) Cytokine and chemokine panel: Increasing of: • Pro-inflammatory cytokines: IFN-γ, IL-6, IL-18, CXCL1, CXCL9, CXCL10, CXCL11, CXCL13, G-CSF • Anti-Inflammatory cytokines: IL-1RA, IL-10 Liver biopsy: cholangio-hepatitis Acute hepatitis with portal inflammation and interface hepatitis, together with focal cholangitis and lobular microgranulomatous reaction. Inflammation mainly composed of T	AST 184 U/L (14-50) ALT 331 U/L (11-50) ALP 1018 U/L (36-108) Gamma-GT 3475 U/L (10-71) Bilirubin 178 µmol/L (0-21) Ferritin 1350 µg/L (30-400) CRP 106 mg/L (<10) ESR >110 mm/h (<10) Infectious panel negative for: HAV, HBV, HCV, HEV, CMV, EBV, VZV, HIV 1/2, TB spot Auto-immune panel negative for: Complement (C3c, C4), ANA and autoantibodies associated with autoimmune liver diseases (anti-smooth muscle, anti-actin, anti-M2, anti-gp210, anti-sp100, anti-LKM1, anti-LC1, anti-SLA) Cytokine and chemokine panel (performed 6 days after starting high-dose CS that probably affected results): Increasing of: • Pro-inflammatory cytokines: IFN-γ-induced chemokines such as CXCL1, CXCL9 and CXCL10 • Anti-Inflammatory cytokines: IL-10 First liver biopsy: cholangio-hepatitis Severe mixed portal inflammation with interface hepatitis, ductular reaction and biliary metaplasia of periportal hepatocytes. Inflammation mainly composed of T lymphocytes, with $CD4^+$ and $CD8^+$ equally represented. Background of alcohol-related	AST 531 U/L (14-50) ALT 1037 U/L (11-50) ALP 636 U/L (36-108) Gamma-GT 1617 U/L (10-71) Bilirubin 40 µmol/L (0-21) Ferritin 3506 µg/L (30-400) CRP 17 mg/L (<10) Infectious panel negative for: HAV, HBV, HCV, HEV, CMV, EBV, VZV, HIV 1/2, TB spot Auto-immune panel negative for: Complement (C3c, C4), ANA and autoantibodies associated with autoimmune liver diseases (anti-smooth muscle, anti-actin, anti-M2, anti-gp210, anti-sp100, anti-LKM1, anti-LC1, anti-SLA) Cytokine and chemokine panel (performed 5 days after starting high-dose CS that probably affected results): Increasing of: • Pro-inflammatory cytokines: IL-7, IL-18 and IFN-γ-induced chemokines such as (CXCL9, CXCL13 and HGF) Liver biopsy: hepato-cholangitis Portal inflammation with some interface hepatitis but mostly with a concentric peribiliary tropism, mainly composed of T lymphocytes, with $CD4^+$ and $CD8^+$ almost equally represented.

	lymphocytes, with $CD4^+$ and $CD8^+$ almost equally represented. Absence of fibrosis.	steatofibrosis. Second liver biopsy after 2 weeks of CS at day 20: predominant cholangitis lesional pattern with altered bile ducts, ductopenia, biliary infarcts. Inflammation mainly composed of T lymphocytes, with $CD4^+$ and $CD8^+$ equally represented.	
Imaging features	PET-CT: no liver metastasis, regression of the mediastinal lymph nodes and shrinkage of the lung mass in the left upper lobe	Abdominal MRI: hepatomegaly and intrahepatic biliary dilatations with enhancement, without choledocal lesion or enlargement.	Abdominal MRI: absence of organomegaly, absence of intra or extrahepatic biliary dilatations
Concurrent irAEs	AIN (AKIN stage II)		
Time point of diagnosis of irCH	After 4 cycles (70 days after starting treatment, 36 days after last dose)	After 4 cycles (123 days after starting treatment, 63 days after last dose)	After 1 cycle (30 days after starting the first dose)
Type and duration of CS therapy	Methylprednisolone: 125 mg/day for 3 days, 500 mg/day for 2 days than 0.5 mg/kg/day for 14 days, than oral prednisone 0.5 mg/kg/day with rapid tapering 14 days to reach ≤ 20 mg of CS per day since the first TCZ	Methylprednisolone started at 62.5-125 mg/day for 11 days than oral prednisone 1 mg/kg/day with rapid tapering 11 day to reach ≤ 20 mg of CS per day since the first TCZ	Methylprednisolone started at 125 mg/day for 5 days, than stop for 2 days, than 125 mg/day for 5 days, than oral prednisone 1 mg/kg for 5 days, than rapid tapering 11^3 day to reach ≤ 0.5 mg/kg of CS per day since TCZ
Additional treatment	TCZ 8 mg/kg iv 2 doses	TCZ 8 mg/kg iv 2 doses	TCZ 8 mg/kg iv 1 dose
Cancer response	PR	PR	

ANA antinuclear Antibody
AIH autoimmune hepatitis
AIN acute interstitial nephritis
ALT alanine transaminase
AST aspartate transaminase
ALP Alkaline Phosphatase
CRP C-reactive protein
ESR erythrocyte sedimentation rate
irAEs immune-related adverse events
IMH immune-mediated hepatitis
CS corticosteroids
TCZ tocilizumab
PR partial remission