Treatment of Hepatitis C in Patients Undergoing Immunosuppressive Drug Therapy

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Abstract

With 185 million people chronically infected globally, hepatitis C is a leading bloodborne infection. All-oral regimens of direct acting agents have superior efficacy compared to the historical interferon-based regimens and are significantly more tolerable. However, trials of both types of regimens have often excluded patients on immunosuppressive medications for reasons other than organ transplantation. Yet, these patients—most often suffering from malignancy or autoimmune diseases—could stand to benefit from these treatments. In this study, we systematically review the literature on the treatment of hepatitis C in these neglected populations. Research on patients with organ transplants is more robust and this literature is reviewed here non-systematically. Our systematic review produced 2273 unique works, of which 56 met our inclusion criteria and were used in our review. The quality of data was low; only 3 of the 56 studies were randomized controlled trials. Sustained virologic response was reported sporadically. Interferon-containing regimens achieved this end-point at rates comparable to that in immunocompetent individuals. Severe adverse effects and death were rare. Data on all-oral regimens were sparse, but in the most robust study, rates of sustained virologic response were again comparable to immunocompetent individuals (40/41). Efficacy and safety of interferon-containing regimens and all-oral regimens were similar to rates in immunocompetent individuals; however, there were few interventional trials. The large number of case reports and case series makes conclusions vulnerable to publication bias. While firm conclusions are challenging, given the dearth of high-quality studies, our results demonstrate that antiviral therapy can be safe and effective. The advent of all-oral regimens offers patients and clinicians greatly increased chances of cure and fewer side effects. Preliminary data reveal that these regimens may confer such benefits in immunosuppressed individuals as well. More prospective interventional trials would greatly benefit the many patients with chronic hepatitis C on immunosuppressive therapies.

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Introduction

Background

More than 185 million people are chronically infected with hepatitis C virus (HCV) globally.1 In the United States and Canada, an estimated 4.4 million persons have chronic HCV infection. Chronic hepatitis C is associated with substantial morbidity and mortality due to progressive liver fibrosis, liver cirrhosis, liver cancer, liver failure and need for liver transplantation. Recent advances in antiviral therapy based on all-oral, interferon (IFN)-free regimens with direct acting antiviral agents (DAAs) have resulted in significant improvements in safety and viral eradication rates, also known as sustained virologic response (SVR). However, outside of the organ transplant context, very limited data are available that address safety and efficacy in patients undergoing immunosuppressive drug therapy. Although clinical trials have addressed specific populations that are immunocompromised, including those with human immunodeficiency virus (HIV) coinfection and post-liver or –kidney transplantation, patients undergoing other forms of immunosuppressive drug therapy in the context of cancer chemotherapy and the treatment of autoimmune conditions have generally been excluded. As such, the available literature addressing these populations has been limited primarily to case reports or series and to historical IFN-based regimens. Due to the high prevalence of autoimmune conditions and cancer in the general population2 and among those with chronic hepatitis C, more evidence-based guidance is needed to inform clinicians of the implications of immunosuppressive drug therapy on HCV treatment. Herein, we report the results of a systematic

Keywords: MeSH termsHepatitis C/drug therapy; Interferons; Direct acting antivirals; Immunosuppressive agents; Chemotherapy.

Abbreviations: SFU, S-fluorouracil; AASLD, American Association for the Study of Liver Diseases; ABX, antibiotics; AE, adverse effect; AIH, autoimmune hepatitis; ALL, acute lymphoblastic leukemia; APASL, Asian Pacific Association for the Study of the Liver; ASAT, aspartate aminotransferase; AST, aspartate transaminase; AT, antiviral therapy; BFM, Berlin-Frankfurt-Münster; CD, Crohn’s disease; CR, complete response; CRP, C-reactive protein; DAA, direct acting antiviral; EASL, European Association for the Study of Liver; EPO, erythropoietin; ESRD, end-stage renal disease; EVR, early viral response; G-CSF, granulocyte-colony stimulating factor; Hb, hemoglobin; HCC, hepatitis C virus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IDSA, Infectious Diseases Society of America; IFN, interferon; IS, immunosuppression; MM, multiple myeloma; MPGN, membranoproliferative glomerulonephritis; MTX, methotrexate; NHL, non-Hodgkin’s lymphoma; NK cell, natural killer cell; NR, no response; PASI, psoriasis area severity index; peg, polyethylene glycol; PLT, platelets; PR, partial response; QD, daily; RA, rheumatoid arthritis; RBV, ribavirin; RNA, ribonucleic acid; SSD, sickle cell disease; SVR, sustained virologic response; TNF-α, tumor necrosis factor-α; TRAIL, TNF-related apoptosis-inducing ligand; UC, ulcerative colitis; VL, viral load; WBC, white blood cells; wnl, within normal limits; XELOX, Xeloda-oxaliplatin.

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review of available literature addressing HCV treatment in patients undergoing pharmacologic immunosuppression, focusing on immunosuppression for purposes other than organ rejection, and identify key gaps in the evidence that form the basis for future research priorities.

**Chronic Hepatitis C in Immunosuppressed Patients**

The immunopathogenesis of HCV infection is complex. Immunosuppression might be expected to reduce host-mediated inflammatory pathways that lead to liver damage; it may also reduce immune defenses against direct virally mediated liver injury. Steroids used in patients with hepatitis C/autoimmune hepatitis (AIH) overlap syndrome have led to clinical, biochemical and histologic improvements, despite an increase in viral load (VL). Inhibitors of tumor necrosis factor-α (TNF-α) appear to be safe for use in patients with HCV. Recent studies have argued that rates of hepatocellular carcinoma (HCC) in patients with HCV who were treated for psoriasis with anti-TNF-α inhibitors are no higher than in those not on TNF-α inhibitors, which raises the possibility of a therapeutic role for TNF-α inhibitors for psoriasis in patients with chronic HCV infection. Among patients with inflammatory bowel disease (IBD) and HCV infection who are on immunosuppressive therapy, the rate of progression of fibrosis is similar to rates reported in patients not on immunosuppressive therapy. 

**Scientific Rationale for Limiting Treatment**

Treatment of HCV in immunosuppressed patients during the IFN era was complicated by varying effects on HCV and the disease being treated with immunosuppressive agents. Immunosuppression can cause worsening of liver dysfunction in patients infected with HCV. Patients on cytotoxic chemotherapy, this may lead to interruption or cessation of chemotherapy, as is reportedly the case for nearly 50% of chemotherapy, as is reportedly the case for nearly 50% of patients. Second, IFN can induce flares of autoimmune hepatitis (AIH) overlap syndrome have led to clinical, biochemical and histologic improvements, despite an increase in viral load (VL). Inhibitors of tumor necrosis factor-α (TNF-α) appear to be safe for use in patients with HCV. Recent studies have argued that rates of hepatocellular carcinoma (HCC) in patients with HCV who were treated for psoriasis with anti-TNF-α inhibitors are no higher than in those not on TNF-α inhibitors, which raises the possibility of a therapeutic role for TNF-α inhibitors for psoriasis in patients with chronic HCV infection. Among patients with inflammatory bowel disease (IBD) and HCV infection who are on immunosuppressive therapy, the rate of progression of fibrosis is similar to rates reported in patients not on immunosuppressive therapy. 

**Transplant Experience**

**Liver Transplant**

The literature supporting the treatment of hepatitis C in liver transplant recipients is more robust than that for patients on immunosuppressive drug therapy for other indications. In patients with HCV prior to liver transplant, recurrence is nearly universal. Historical IFN-based regimens used in patients with recurrent post-transplant HCV were poorly tolerated and associated with low rates of SVR. A systematic review of IFN-based treatment in liver transplant recipients on immunosuppressive regimens (mostly comprised of tacrolimus, cyclosporine and corticosteroids) revealed pooled SVR rates (24% and 27% with IFN/RBV and pegylated IFN/RBV, respectively). Acute rejection occurred in 2% to 5% of patients, and a least two-thirds required dose reduction or early discontinuation. More recent reports cite SVR rates that are lower than 50% and acute rejection rates that are not significantly higher than those achieved with placebo.

Updated consensus guidelines of the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) now recommend all-oral treatment of hepatitis C in liver transplant recipients. Randomized controlled trials have found SVR rates of over 90% in post-transplant patients with F0–F3 fibrosis and compensated cirrhosis, and of 80–85% in post-transplant patients with Child B or C decompensated cirrhosis undergoing...
antiviral therapy with sofosbuvir/ledipasvir or sofosbuvir/daclatasvir.44,55,56 Serious adverse effects attributed to antiviral therapy were rare, and both regimens were well tolerated. Drug-drug interactions between DAAs and immunosuppressive drugs such as tacrolimus and cyclosporine are common, and require careful attention prior to and throughout the treatment course.

**Kidney Transplant**

No drugs are currently approved for the treatment of hepatitis C in kidney transplant recipients. IFN-containing regimens are generally avoided in renal transplant recipients because of an increased risk of graft rejection. A 2014 meta-analysis showed that IFN-containing regimens achieved SVR in 34%, but approximately one-third of patients failed to complete the treatment course, of whom approximately half discontinued due to graft dysfunction.57 Accordingly, renal society guidelines from the IFN era suggest treating hepatitis C in renal transplant recipients only when the benefits outweigh the significant risk of rejection from IFN (e.g. fibrosing cholestatic hepatitis, cirrhosis or life-threatening vasculitis).58 These guidelines suggested that although conventional immunosuppression can be used in this context, the evidence base to support specific therapies post-renal transplant is largely of very low quality, including case reports and case series.

Recent reports do suggest that all-oral DAA regimens appear to be well tolerated and efficacious in patients following renal transplantation.59-62 One randomized controlled trial by Colombo et al63 reported at the International Liver Congress in April 2016 revealed that sofosbuvir/ledipasvir for 12 or 24 weeks was associated with an SVR of 98% (112/114) in GT1 or 4 treatment-naive or experienced patients post-renal transplant, and was associated with favorable safety, with no events of acute rejection.

**Other Transplant**

We are aware of no studies examining the treatment of hepatitis C in recipients of other types of solid organ transplants. We were also unable to find studies in patients who had received stem cell transplants. One series of hepatitis C treatment in patients who had received bone marrow transplants excluded patients on immunosuppressive drug therapy.64 A letter to the editor reports outcomes of five patients treated for hepatitis C after autologous stem cell transplantation but does not report immunosuppressive regimens that were used.65

**Methods**

We conducted a systematic search of Medline (OVID), Cochrane Library, Embase and CINAHL in February 2016 for publications with the following terms: antineoplastic protocols, chemotherapy, antineoplastic agents, neoplasms/drug therapy, immunosuppressive agents, glucocorticoids, TNF-α, calcineurin inhibitors, and hepatitis c/drug therapy. We excluded citations with the keyword “organ transplantation” and limited our search to English language articles. Conference abstracts from the AASLD, the European Association for the Study of Liver (EASL), and the Asian Pacific Association for the Study of Liver (APASL) from 2015 and 2016 were reviewed in a targeted fashion, and one abstract from an international conference in February 2016 was included.66

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Long-term steroid regimens with more than 20 mg of prednisone equivalent per day were considered to be immunosuppressive. Patients who received rituximab administrations as early as 1 month before initiation of antiviral therapy were included. Otherwise, administration of any immunosuppressive agent while the patient was being treated for HCV was considered to be concomitant with antiviral therapy. Trials without clear description of the timing of drug therapy were excluded. Pharmacologic dosing trials were excluded as well.

Studies were characterized by their study design (e.g. randomized controlled trial), sample size, treatment regimens and outcomes. Outcomes for the disease for which immunosuppressive therapy was administered was judged to be positive if partial response or complete response was achieved or if otherwise described as being generally positive. If the treatment was repeated due to relapse, we chose to report the results of the first course only.

SVR was defined as undetectable HCV RNA at 12 weeks after the end of treatment for all-oral, IFN-free regimens, and 24 weeks after the end of treatment for historical IFN-based regimens. If RNA levels were not reported at 24 weeks but were reported at a later time point (e.g. at 36 weeks after the end of treatment) SVR at that point was used. Reports on cryoglobulinemic vasculitis are reported separately (i.e. not grouped by agent), as multiple classes of immunosuppressive therapies were often used and the primary intent of IFN-based treatment was as much treatment of vasculitis as treatment of HCV infection per se.

**Results**

**Literature Search Results**

A total of 2916 citations were retrieved through our search of the databases (Fig. 1). Of these, 143 were duplicates, leaving 2273 unique works. Abstracts from four international society meetings (AASLD, EASL, APASL, and Digestive Disease Week) were also reviewed to identify relevant studies, contributing one abstract from February 2016.66 The studies were screened by KO and 96 studies were identified as possibly meeting criteria. After further review, 56 were included in this systematic review (Fig. 1). The studies selected for this review included 8 prospective interventional studies (n = 185 patients), including 3 randomized controlled, trials (n = 76 patients), one non-randomized controlled trial (n = 76 patients), and four other prospective interventional trials (n = 33 patients). The studies also included 4 prospective cohort studies (n = 84 patients), 15 retrospective cohort studies, case-control studies, and case series (n = 80 patients), and 29 case reports (n = 33 patients). Approximately 40% of studies addressed cryoglobulinemia (Table 2). Ten studies comprising only 19 patients reported the results of cancer patients. Five studies with an average of 31 patients each reported the results of immunosuppressive agents used for the treatment of hepatitis C. IBD and other autoimmune disorders (e.g. rheumatoid arthritis) made up the remainder (19 studies and 93 patients).

**Cryoglobulinemia and Vasculitis**

In HCV-associated cryoglobulinemic vasculitis, B-cell expansion causes elevated levels of immunoglobulins that in turn can lead to skin ulcers, renal disease, neuropathy and other
symptoms. Both IFN-based antiviral therapy and immunosuppressive agents (e.g. rituximab) are components of regimens used to treat HCV-associated vasculitis. A number of studies have investigated the use of combination antiviral therapy and anti-CD20 antibodies to treat HCV-associated cryoglobulinemia, vasculitis or a combination of the two. As the primary intent is resolution of symptoms and organ dysfunction, rather than treatment of HCV, clinical response of renal function, skin ulcers and other manifestations of vasculitis are often described in detail but viral response rates, including SVR, are often not reported. Nonetheless, we can assess the efficacy and safety of anti-HCV agents used concomitantly with immunosuppressants in these settings.

In total, 22 studies reported outcomes of 116 patients (Table 3). In the nine studies that reported VL at 24 weeks after treatment or later, on aggregate, 56% of patients achieved SVR; this finding was roughly similar to the usual efficacy of the various IFN-based regimens used in these studies. Nine patients required cessation or interruption of therapy secondary to adverse effects related to the medications. In the three studies with more than 10 patients, 46 of 80 patients (58%; range, 55–59%) reached SVR; all three used rituximab with pegIFN and RBV. Similarly, clinical response of the cryoglobulinemia was seen in 84 of the 110 patients (76%). Adverse effects of IFN, RBV and rituximab did not appear to be more common than in patients not on immunosuppressive therapy.

In a prospective cohort study of 38 patients on rituximab and various corticosteroids, other immunosuppressive agents or plasma exchange, three patients died (cirrhosis, liver carcinoma, unknown) but mortality was not significantly different from the control group (2/55 died from liver carcinoma).

Few studies report the use of DAAs in cryoglobulinemia or vasculitis. Humphries et al reported a case of cryoglobulinemic vasculitis manifesting as membranoproliferative glomerulonephritis (MPGN) and skin ulcers that was treated

| Study Design                  | Studies | Patients |
|------------------------------|---------|----------|
| Case report                  | 29      | 33       |
| Case series                  | 10      | 44       |
| Case-control                 | 2       | 11       |
| Retrospective cohort         | 3       | 25       |
| Prospective cohort           | 4       | 84       |
| Prospective interventional   | 4       | 33       |
| Non-randomized controlled    | 1       | 76       |
| Randomized controlled trial  | 3       | 76       |
| **Total**                    | **56**  | **382**  |

| Reason for Immunosuppression | Studies | Patients |
|------------------------------|---------|----------|
| Cryoglobulinemia/vasculitis  | 22      | 116      |
| Cancer                       | 10      | 19       |
| HCV – trial                  | 5       | 154      |
| IBD                          | 8       | 60       |
| Autoimmune – Other           | 11      | 33       |
| **Total**                    | **56**  | **382**  |
| Study            | Type                  | n  | Age | Male, % | Immunosuppression                                      | AT                          | Outcomes                           | Adverse Effects                                                                 | SVR, % | Clinical Response, % |
|------------------|-----------------------|----|-----|---------|---------------------------------------------------|-----------------------------|------------------------------------|---------------------------------------------------------------------------------|--------|----------------------|
| Sise, 2016       | Case series           | 5  | N/A | N/A     | Rituximab × 4 pts                                 | Sofosbuvir + ribavirin or sofosbuvir + simeprevir × 12 wks | SVR12 in 3/4 pts on rituximab and 0/1 pts on ustekinumab (relapsed)       | Not reported separately                                                                 | 60     |                      |
| Saadoun, 2014    | Prospective cohort    | 4  | N/A | N/A     | Rituximab given 1 mo before AT                     | pegIFNα + RBV × 48 wks + telaprevir × 12 wks or boceprevir × 44 wks | PR in 2/4 and CR in 2/4          | Not reported separately                                                                 | 100    |                      |
| Humphries, 2014  | Case report           | 1  | 59  | 100%    | Methylprednisolone 500 mg × 2d and plasmapheresis × 5 | Telaprevir, IFN, RBV × 24 wks | PR. Progressed to ESRD on HD 7 wks after end of tx. SVR achieved | Anemia requiring transfusions, EPO, and interruption of IFN and RBV            | 100    | 0%                   |
| Wu, 2013         | Case report           | 1  | 57  | 0%      | Methylprednisolone 40 mg/d started with AT         | PegIFN α-2b + RBV           | Thrombocytopenia resolved. Renal function improved. Cryoglobulins persistently high | None reported                                                                 | 100    |                      |
| Zaidan, 2012     | Case report           | 2  | 44  | 50%     | Nodules resolved. Renal function normalized but the relapsed | PegIFN-α-2a + RBV           | Case 3: HCV: SVR at unknown time point. Purpura resolved. Renal function PR. Case 4: Skin lesions resolved. Renal function recovered | None reported                                                                 | 100    |                      |
| Rodrigo, 2012    | Case report           | 1  | 34  | 100%    | Prednisolone 10 mg BID + cyclophosphamide         | PegIFN-2α + RBV             | Skin lesions healed. Weakness improved. No relapse in 6 mo                 | None reported                                                                 | 100    |                      |
| Kiremitci, 2012  | Case report           | 1  | 34  | 0%      | Methylprednisolone 0.5 mg/kg/d started with AT    | PegIFN α2                 | Nodules resolved. Renal function normalized but the relapsed                | None reported                                                                 | 0      |                      |
### Table 3. Cryoglobulinemia and vasculitis (continued)

| Study          | Type               | n  | Age | Male, % | Immunosuppression                                                                 | AT                              | Outcomes                     | Adverse Effects                                                                 | SVR, % | Clinical Response, % |
|----------------|--------------------|----|-----|---------|-----------------------------------------------------------------------------------|---------------------------------|------------------------------|--------------------------------------------------------------------------------|--------|----------------------|
| Colucci, 2011  | Case report        | 1  | 53  | 0%      | Rituximab before and cyclosporin A concurrent with AT                              | PegIFN × 12 mo                  | SVR not achieved             | No fever, pain or allergic reactions                                        | 0%     |                      |
| Butterly, 2010 | Case series        | 1  | 44  | 100%    | Rituximab                                                                        | PegIFN                          | No improvement in vasculitis |                                                                         | 0%     | 0%                   |
| Saadoun, 2010  | Prospective cohort | 38 | 58  | 32%     | Rituximab +/− concurrent steroids, other immunosuppressive agents or plasma exchange | PegIFN−2a or 2b + RBV × 48 wks  | Similar SVR (22/38 vs 33/55 in control). Shorter time to clinical remission Higher rates of CR (28/38 vs 40/55) and PR (9/38 vs 13/55). 3 Deaths (cirrhosis, liver carcinoma, unknown) (no diff compared to cntl) | AE from AT in 21 and from rituximab in 10. Treatment interrupted in 5/38 (cytopenia × 2, depression, psoriasis flare, neuropathy flare) (5/55 in control) | 58%    | 79%                  |
| Dammacco, 2010 | RCT                | 22 | 63  | 32%     | Rituximab + methylprednisolone prior to and during AT                              | PegIFN−2a or 2b + RBV × 48 wks  | SVR (13/22 vs 4/15 in control). Higher CR (12/22 vs 5/15), Lower PR (5/22 vs 5/15). Relapses (2/22 vs 3/15) | Cytopenias, fevers, other mild AEs                                         | 68%    | 77%                  |
| Terrier, 2009  | Retrospective cohort| 20 | 61  | 30%     | Rituximab. Some also received CS or plasmapheresis                                | PegIFN−2b + RBV starting 1 mo after last rituximab. × 12 mo (median) | Higher SVR (11/20 vs 0/12 in control). Higher clinical response of vasculitis: CR 16, PR 3, NR1, relapse 3 (7/12, 1/12, 4/12, 4/12 in Cntl) | Generally well tolerated                                                     | 55%    | 80%                  |
| Ahmed, 2008    | Case report        | 1  | 35  | 100%    | Methylprednisolone before AT. Prednisone PO 40 mg/d started with AT                 | PegIFN ≥ 3 mo                   | Renal function improved. Albumin still elevated (38 g/L)                     | None major                                                                     | 100%   |                      |
| Koziolek, 2007 | Case report        | 1  | 38  | 0%      | Prednisolone 1 mg/kg started −3 mo before AT. Cryoprecipitate after starting AT    | PegIFN + RBV                    | Arthralgias and proteinuria improved                                          | Symptomatic anemia. RBV stopped                                              | 100%   |                      |
| Study                  | Type                  | n | Age | % | Male, | Immunosuppression         | AT                              | Outcomes                               | Adverse Effects                          | SVR, % | Clinical Response, % |
|------------------------|-----------------------|---|-----|---|-------|---------------------------|-----------------------------------|----------------------------------------|-----------------------------------------|--------|----------------------|
| Saadoun, 2006<sup>131</sup> | Prospective cohort   | 4 | N/A | N/A | 50%   | Rituximab                 | pegIFN-α-2b/IFN-α2b + RBV x ≥6 mo | Clinical response in 1/4                | Undear                                | 25%    |                      |
| Saadoun, Aids 2006<sup>132</sup> | Retrospective cohort | 2 | 47  | 50% |       | Case 7: IVIG (2 g/kg/mo) + corticosteroids only | INF-α + RBV x ≥6 mo | Case 7: relapse to IFN-RBV, no SVR, no response to IS Case 8: CR to IFN-RBV, SVR, no response to IS | None following immunosuppression | 50%    | 50%                  |
| Neri, 2005<sup>133</sup> | Case report           | 1 | 63  | 0%  |       | Cyclophosphamide + prednisone | pegIFN-α2b | Symptomatic improvement. Died 4 mo later of nephritic syndrome and sepsis. SVR not achieved | None | 0% 0%                |
| Mendez, 2001<sup>134</sup> | Case report           | 2 | 46  | 100% |       | Case 4: plasmapheresis + IVIG Case 6: plasmapheresis + corticosteroids | IFN | Case 4: “Improved clinically and … doing well.” Case 6: Necrotizing vasculitis responded. Hepatitis and viremia persisted. Died of MI 7y later | None reported | 100%               |
| Cacoub, 2001<sup>135</sup> | Case control          | 5 | N/A | N/A |       | Prednisone (1 mg/kg/d) reduced to 10 mg/d. Plasma exchange x 12 | IFN-α x 18–36 mo | Complete recovery in 5/5 (except ESRD in 1). No deaths | None reported | 100%               |
| Mercie, 2000<sup>94</sup> | Case report           | 1 | 40  | 0%  |       | Corticosteroid bolus monthly and “oral corticosteroids” (1 mg/kg/d) slowly tapered | IFN x 18 mo | HCV relapsed. Favorable course of vasculitis without reactivation | None reported | 0% 100%            |
| Kiyomoto, 1999<sup>136</sup> | Case report           | 1 | 69  | 0%  |       | Cryofiltration + prednisolone 30 mg/d | IFN-α | Renal function deteriorated. Nephrotic syndrome recurred | Flu-like symptoms, pancytopenia. Fever caused a 1 wk interruption | 0%     |                      |
| David, 1996<sup>137</sup> | Case report           | 1 | 39  | 100% |       | Prednisone 100 mg/d + azathioprine x −10 d. Plasmapheresis + cyclophosphamide later added | IFN-α x 8 mo | No new symptoms while on IFN. Strength started improving after 5–6 mo | Hemorhagic cystitis. Cyclophosphamide DCed | 100%    |                      |
with telaprevir, pegIFN and RBV concurrent with methylprednisolone and plasmapheresis. SVR was achieved, but the MPGN progressed to end-stage renal disease by 7 weeks after treatment. The case was also complicated by anemia requiring interruption of treatment and transfusions of packed red blood cells. In a prospective cohort study of telaprevir or boceprevir and pegIFN and RBV in four patients who had been treated for mixed cryoglobulinemic vasculitis with rituximab 1 month prior, two patients achieved partial response and two achieved complete response;⁷⁵ SVR was not reported.

In the only study addressing the use of an all-oral regimen, three out of four patients on rituximab treated with sofosbuvir with RBV or simeprevir achieved SVR12.⁷⁶ One patient on three out of four patients on rituximab treated with sofosbuvir adverse effects were reported. In three of four patients for which it was reported. No major prescription of inflammatory cytokines.⁷⁷ Withdrawal of steroids infiltration into sites of tissue damage and repress tran-
mitsive effects at higher doses. They inhibit leukocyte Glucocorticoids have potent anti-inflammatory and immuno-
suppressive effects at higher doses. They inhibit leukocyte infiltration into sites of tissue damage and repress tran-
scription of inflammatory cytokines.⁷⁷ Withdrawal of steroids can cause these inflammatory processes to rebound. Some have investigated the use of this phenomenon for the treat-
ment of HCV infection with mixed effects.⁷⁸–⁸⁰

The effect of steroids can be clouded by other immuno-
suppressive agents that are frequently administered concom-
itantly. Five case reports discuss high-dose steroids used in the absence of other immunosuppressive therapies and concomitantly with antiviral therapy (Table 4).⁸¹–⁸⁵ Three studies reported on patients with MPGN and/or vasculitis; three of four patients achieved a favorable clinical response and one of two achieved SVR.⁸¹–⁸⁴ Overall, SVR was achieved in three of four patients for which it was reported. No major adverse effects were reported.

Efe et al⁸⁶ reports the results of a retrospective study of patients with HCV infection and AIH. Thirteen patients received immunosuppression with prednisone at a dose of 20–40 mg/day. An unknown number of these patients received azathioprine as well. After 3–6 months of immuno-
suppression, levels of alanine transaminase and aspartate transaminase fell below twice the upper limit of normal, and antiviral therapy with IFN with or without RBV was initiated. SVR was achieved in 7/13 and no relapse of AIH was observed. A report of two patients with AIH and HCV treated with pegIFN–α2b and RBV while taking 20 mg/day of predni-
solone reported achievement of SVR and good clinical response for both.⁸⁵ Overall, the use of glucocorticoids with IFN-based regimens achieved SVR in 10 of 17 patients (59%).

Based on these reports, treatment of chronic HCV infection with IFN-based regimens in patients on immunosuppressive doses of corticosteroids appears as safe and as effective as in patients not on immunosuppression. This conclusion should be considered in light of the caveat that the data is sparse and of low quality. A single case series accounts for 13 of 19 total patients in these studies. Furthermore, these conclusions have become less relevant with the advent of DAAs. Unfortunately, there are no reports of all-oral DAA regimens used in patients on glucocorticoids in the absence of other immuno-
suppressive agents.

**Cytotoxic Chemotherapy for Cancer**

Treatment of chronic HCV infection in patients on chemotherapy for cancer presents a unique challenge and opportunity. Cir-
rhosis and chronic hepatitis are reportedly three-fold more common in those with cancer than in the general population.⁸⁷ Studies in patients with hematological malignancies suggest the prevalence of chronic HCV infection may range between 1.5% and 32%, depending on the type of malignancy and the population studied.⁸⁸ Chronic infection with HCV is associated with 1.6-fold [lung cancer; non-Hodgkin’s lymphoma (NHL)] to 48.6-fold (liver cancer) increased risk of cancer.⁸⁹ AASLD guidelines do not address treatment of HCV in patients with cancer other than to recommend against monitoring for HCV recurrence in patients who achieved SVR.³⁴ Large trials of anti-
 viral therapy for HCV have excluded patients on chemotherapy, making the literature on this topic sparse.

Seven studies with a total of 11 patients describe IFN-
based regimens administered concomitantly with cytotoxic chemotherapy for patients with cancer (Table 5). All but one is a case report. Six patients had solid tumors (colon, breast, HCC) and five suffered from hematologic malignancies [acute lymphoblastic leukemia (ALL), NHL, multiple myeloma (MM)]. In the largest study, 5-fluorouracil (5FU) was infused into the hepatic artery in four patients with HCC.⁹⁰ Partial response of the HCC was seen in all patients. SVR was not reported. Overall, three of five (60%) patients in whom SVR was reported achieved this end-point. In two studies, HCV VL was undetectable at an unknown time point and SVR was not explicitly reported.⁹⁰,⁹¹ One study reported achieving early virologic response but antiviral therapy was ongoing.⁹² Taken in aggregate, the studies reported positive clinical responses in 10 of 11 patients. In six patients with hematological malignancies, four (ALL in three, B-cell NHL in one) experienced remission. In a case report of MM, disease progressed to involve new compression fractures at 4 months after thalidomide was initiated.

Adverse events were generally mild and limited to those known to be associated with the agents used. Cyto-
penias were common in patients with hematological malignancies. In three studies (three patients total), therapy was interrupted or modified as a result. In one study of docetaxel and trastuzumab for breast cancer, grade 4 neutropenia and grade 3 hepatotoxicity caused a delay in antiviral therapy and chemotherapy.⁹² While these reports give us some sense of possible out-
comes, it is undoubtedly too little to give clinicians much confidence when contemplating the treatment of HCV in their patients on cytotoxic chemotherapy. The paucity of data on this topic is especially unfortunate given that cancer is a relatively prevalent disease and that cytotoxic chemotherapy has long been a mainstay of therapy. Significantly, no studies report the use of modern all-oral DAA regimens in patients on cytotoxic chemotherapy for cancer.
| Study          | Type       | n  | Age % | Reason for IS                  | Immunosuppression     | AT                  | Outcomes                                                                 | Adverse Effects | SVR, % | Clinical Response, % |
|---------------|------------|----|-------|--------------------------------|-----------------------|---------------------|--------------------------------------------------------------------------|-----------------|--------|----------------------|
| Wu, 2013     | Case report| 1  | 57    | 0% Cryoglobulinemia - MPGN     | Methylprednisolone 40 mg/d | PegIFN-α2b + RBV   | Thrombocytopenia resolved. Renal function improved. Cryoglobulins persistently high | None reported   | 100%   |                      |
| Kiremitci, 2012 | Case report | 1 | 34    | 0% Cryoglobulinemia - MPGN, skin eruptions, pneumonitis | Methylprednisolone 0.5 mg/kg/d | PegIFN-α2 | Nodules resolved. Renal function normalized but the relapsed | None reported   | 0%     |                      |
| Ahmed, 2008  | Case report | 1 | 35    | 100% MPGN type 1. Cryoglobulin negative | Methylprednisolone before AT. Prednisone 40 mg/d started with AT | PegIFN-α, RBV added after 3 mo | Renal function improved. SVR. Albumin still elevated (38 g/L) | None major      | 100%   | 100%                 |
| Mercie, 2000 | Case report | 1 | 40    | 0% Churg Strauss               | Corticosteroid bolus monthly and "oral corticosteroids" (1 mg/kg/d) slowly tapered | IFN × 18 mo          | HCV relapsed. Favorable course of vasculitis without reactivation | None reported   | 0%     | 100%                 |
| Oeda, 2012   | Case report | 2 | 50    | 0% AIH + HCV                   | Prednisolone 30–40 mg/d prior to AT reduced to 20 mg/d when AT started | PegIFN-α2b + RBV × 24–48 wks | SVR in 2/2. ALT and IgG normalized in 2/2. | None reported   | 100%   | 100%                 |
| Efe, 2013    | Case series | 13| N/A NA | AIH + HCV                      | Prednisone 20–40 mg/d +/- azathioprine | INF +/- RBV          | HCV: SVR in 7/13, NR in 6/13. No relapse of AIH | 54%             | 100%   |                      |
| Study                        | Type                             | n | Age | Male, % | Reason for IS | Immunosuppression | AT     | Outcomes                      | Adverse Effects                                                      | SVR, % | Clinical Response, % |
|------------------------------|----------------------------------|---|-----|---------|---------------|-------------------|--------|-------------------------------|---------------------------------------------------------------------|--------|----------------------|
| Matovina-Brko, 2014<sup>92</sup> | Case report                      | 1 | 60  | 0%      | Breast cancer | Docetaxel + trastuzumab × 1 y and radiotherapy | IFN-α2a + RBV × 6 mo | EVR. No active disease, complications, or HCV | Grade 4 neutropenia and grade 3 hepatotoxicity × 1 wk (AT and chemo delayed) |        | 100%                 |
| Gentile, 2013<sup>138</sup>   | Case report                      | 1 | 60  | 100%    | Colon cancer (adjunct) | XELOX (capecitabine + oxaliplatin) | IFN-α2a | SVR                           | Diarrhea and neuropathy (both grade 1). Cytopenias with nadirs WBC 2.38, Hb 10.5, PLT 81,000. No transaminitis | 100%   | 100%                 |
| Ayyub, 2011<sup>139</sup>     | Case report                      | 1 | 22  | 100%    | ALL           | Vincristine + 6-MP (Patient had been on MTX and dexamethasone) | PegIFN-α2a + RBV × 72 wks | SVR Remission of ALL | Neutropenia requiring IFN reduction and filgrastim |        | 100%                 |
| Papaevangelou, 2010<sup>140</sup> | Case report                      | 2 | 9   | 100%    | Pt 1: ALL Pt 3: B-NHL | Pt 1: ALL BFM 95 Pt 3: NHL BFM 95 | IFN-α a + RBV. 18–24 mo | SVR 1/2. Both patients in remission. | Pt 1: Fever after IFN. Pt 3 transient subclinical hypothyroid |        | 50%                  |
| Kasai, 2009<sup>90</sup>      | Prospective interventional study | 4 | 68  | 75%     | HCC           | 5FU - intraarterial to hepatic artery (250 mg/d) days 1–5 of each week | PegIFN-α2b + RBV × 8–20 wks | HCV VL undetectable in 4/4 at unclear time point. PR of HCC in 4/4. No deaths | Thrombocytopenia × 1. Leukopenia /anorexia × 1 |        | 100%                 |
| Lakatos, 2006<sup>91</sup>    | Case report                      | 1 | 50  | 0%      | Multiple myeloma | Thalidomide begun 2 mo before IS | PegIFN-α2b + RBV × 12 mo | EVR, ETR. New compression fractures | None reported |        | 0%                   |
| Waldron, 1999<sup>141</sup>   | Case report                      | 1 | 11  | 100%    | ALL (b-cell precursor) | Etoposide, Ara-C, cyclophosphamide, vincristine, prednisone × 24 wks | IFN-α | No SVR. ALL in remission 72 mo after | Neutropenia and thrombocytopenia requiring dose adjustments |        | 0%                   |
| Study                 | Type             | n   | Age | Male, % | Reason for IS       | Immunosuppression       | AT                         | Outcomes                                      | Adverse Effects                                      | SVR, % | Clinical Response, % |
|----------------------|------------------|-----|-----|---------|---------------------|------------------------|----------------------------|-----------------------------------------------|-------------------------------------------------|--------|----------------------|
| Torres, 2015<sup>68</sup> | Case-control     | 6   | N/A | N/A     | Various cancers     | Trastuzumab, tamoxifen, letrozole | IFN +/- RBV +/- nitazoxanide | SVR in 3/6 (2/3 trastuzumab, 1/2 tamoxifen, 0/1 letrozole). Not sig different from pts in study not on IS | Not reported separately | 50%    |                       |
| Kyvernitakis, 2014<sup>93</sup> | Case series      | 1   | 34  | 0%      | Mycosis fungoides   | Photopheresis and denileukin diftitox (diptheria toxin + IL2) | IFN-a × 18 mo            | Skin lesions and pruritis improved. Circulating peripheral CD4 +/-CD26− clonal T cells fell from 96.1% to 50.9%. SVR not achieved | Headaches and non-compliance led to multiple interruptions of IFN | 0%     | 100%                 |
| Davar, 2015<sup>94</sup>  | Case report      | 1   | 59  | 0%      | Advanced melanoma   | Pembrolizumab × 15 cycles | Ledipasivir + Sofosbuvir started after cycle 9 of pembrolizumab | Melanoma: “excellent PR.” Undetectable HCV VL and normal ALT and AST after 6 additional cycles of pembrolizumab | None reported                                     | 100%   |                       |
Other Immunosuppressive Agents in Cancer

In a study examining IFN-based antiviral therapy in the setting of various hormonal agents (trastuzumab, tamoxifen, letrozole), SVR was achieved in 3 of 6 patients (Table 6).88 Kyvernitakis et al93 describe the use of IFN in a patient on treatment with photopheresis and denileukin diffitox for mycosis fungoides; skin lesions improved in this study, but SVR was not achieved. One case report describes all-oral antiviral regimens in patients undergoing immunotherapy for cancer.94 Pembrolizumab combined with ledipasvir and sofosbuvir in a patient with advanced melanoma led to “excellent” response, normal transaminases and undetectable VL at an unknown time point. It should be noted that although antiviral therapy was started, at 9 cycles into a 15-cycle course of pembrolizumab it was not completely clear if pembrolizumab was continued while the patient was treated for HCV infection. However, given the novelty of the case—immunotherapy given concomitantly with DAAs—we felt somewhat compelled to include it.

Trials of Immunosuppressive Agents for the Treatment of HCV Infection

Three interventional studies comprising 97 patients examined the use of thalidomide and cyclosporin A for the treatment of HCV infection (Table 7). SVR was achieved in 42/76 (55%) patients in the largest study, a non-randomized controlled trial of cyclosporin A and IFN-α2b compared to IFN-α2b alone.95 There was no significant difference in discontinuation of therapy or adverse events. Two single-armed prospective interventional trials of chemotherapeutic agents and IFN for the treatment of HCV infection were unable to achieve SVR. In a trial of cyclosporin and IFN-αcon-1, hypertension and neutropenia required dose reductions of cyclosporin and IFN respectively.96 In a trial of thalidomide and pegIFN-α2b with RBV, thalidomide was discontinued in 2 of 11 patients due to vasovagal syncope and delirium.97 Overall, it appears that the addition of cytotoxic chemotherapy reduces the efficacy of IFN-based antiviral therapy.

TNF-α Inhibitors

TNF-α is an inflammatory cytokine involved in the expression of other pro-inflammatory cytokines. Inhibitors of TNF-α are routinely used for the treatment of autoimmune disorders, such as IBD, rheumatoid arthritis and psoriasis. These agents, however, have been associated with an increased risk of serious infectious diseases, but data regarding worsening of HCV infection are conflicting.98–101 In a review of 216 patients (260 patient-years of follow-up) with HCV infection treated with TNF-α inhibitors, these agents were withdrawn due to suspected worsening HCV infection only three times.98–101

Five reports on TNF-α inhibitors describe etanercept being used with IFN-based treatments in a total of 25 patients (Table 8).13,102–105 Flares of underlying autoimmune disorders were rare—one patient had a flare of rheumatoid arthritis and one patient experienced a recurrence of neuralgia. A trial of etanercept in combination with IFN and RBV for the treatment of HCV achieved SVR in 8 of 19 patients (42%), which was somewhat higher than in the control group (8/25, 32%) who were treated with IFN and RBV only.105 Two of 19 patients withdrew because of adverse effects, although nausea was less common than in a control group. Otherwise, SVR was
| Study | Type | n | Age | Male, % | Immunosuppression | AT | Outcomes | Adverse Effects | SVR, % |
|-------|------|---|-----|--------|-------------------|----|----------|----------------|--------|
| Basu, 2016 | Controlled trial | 35 | 50 | 74% | Various TNF-α inhibitors | LDV + SOF + RBV × 8 wks or LDV + SOF × 12 wks | SVR12 in 34/35 (100% study retention) | Anemia to Hb < 8.5 in 2/35. Severities of other AE are unclear. | 97% |
| Bartalesi, 2013 | Case report | 1 | 53 | 100% | Etanercept 50 mg 2 × /wk then 1 × /wk | PegIFN-α 2a + RBV | SVR. Psoriasis much improved (PASI 18.9 → > 3.0) | Recurrence of glossopharyngeal neuralgia requiring surgical nerve excision. Anemia for which the pt received EPO. Neutropenia (850/mm³) | 100% |
| Navarro, 2013 | Cohort study | 3 | 47 | 100% | Etanercept | IFN + RBV | Psoriasis improved in 2/3. HCV VL became undetectable in 2/2 with VL measurements. AST and ALT improved in 3/3 | No significant AEs. No sx of hepatitis while on IS | |
| Behnam, 2010 | Case report | 1 | 56 | 100% | Etanercept 50 mg/ wk | IFN-α + RBV × 24 wks | Psoriasis was stable. Liver enzymes and HCV VL decreased markedly | None reported | |
| Jazwinski, 2011 | Case report | 1 | 53 | 100% | Etanercept 50 mg/ wk. Prednisone × 6 d for RA flare | PegIFN-α + RBV × 24 wks | SVR. RA flared after starting AT | RA flare | 100% |
| Zein, 2005 | Randomized controlled trial (phase 2) | 19 | 44 | 90% | Etanercept 25 mg 2 × /wk | IFN-α 2b × 24–48 weeks | SVR in 8/19 (8/25 in control patients on IFN + RBV only). Greater decline in fibrosis compared to control | 2/19 withdrew 2/2 anemia and IFN allergic reaction. (1 withdrew from control). Other AEs similar except nausea was less common with etanercept | 42% |
reported only in two case reports. In a report of rheumatoid arthritis treated with etanercept concomitantly with pegIFN-α and RBV, SVR was achieved but initiation of antiviral therapy was followed by a flare of rheumatoid arthritis that required steroids.104 A patient with psoriasis treated with etanercept concomitantly with pegIFN-α and RBV achieved SVR and improvement in the symptoms of psoriasis, but glossopharyngeal neuralgia recurred and required surgical nerve excision.103 Taken together, the results of these studies show that IFN-based treatments can be given to patients on TNF-α inhibitors, but flares of underlying autoimmune diseases can occur. Moreover, one study has an outsized influence on the results due to the absence of other studies with large numbers of patients.

In an abstract addressing all-oral DAA regimens, Basu et al66 report the results of a controlled trial in which a predominantly male (26/35, 74%) and ethnically diverse group of patients on various TNF-inhibitors for IBD who were treated with ledipasvir and sofosbuvir for 12 weeks (n = 18) or in combination with RBV for 8 weeks (n = 17). All patients completed antiviral therapy and SVR12 was achieved in 34 of 35 total patients. Adverse effects were common and similar between the two groups, except for anemia, which was more common in the RBV group (8/17 vs 2/18). Overall, gastrointestinal discomfort and diarrhea were experienced by 15 and 4 patients respectively. This is an important trial both for its study design and because of the use of modern treatment regimens. Its findings should give clinicians greater confidence in administering these antiviral treatments to patients on TNF-α inhibitors.

**Antimetabolites**

Azathioprine is a purine analog and prodrug of mercaptopurine. These compounds inhibit DNA synthesis, particularly in leukocytes, and thus inhibit inflammation.106 Three studies examined the use of azathioprine in patients treated with IFN-based regimens (Table 9). Results were mixed. In a case series of patients with IBD, one of three patients achieved SVR and two patients required steroids for flares of Crohn’s disease.107 In a case report of a 54-year-old man treated with azathioprine, prednisone, pegIFN and RBV for AIH-HCV overlap syndrome, AIH went into remission but HCV VL never reached undetectable levels.108 The patient developed respiratory failure secondary to Pseudomonal pneumonia and both immunosuppression and antiviral therapies were discontinued.

Adverse effects from concomitant use of RBV and azathioprine can be severe. In a retrospective study of eight patients on IFN, RBV and azathioprine who developed severe pancytopenia, erythropoietin (EPO), packed red blood cells and granulocyte-colony stimulating factor (G-CSF) were required in seven, two, and five patients respectively.109 Time to recovery ranged from 4 to 7 weeks.

Methotrexate inhibits the metabolism of folate, which is required for nucleoside synthesis. In addition to this canonical function, methotrexate may also exert a direct immunosuppressive effect by inhibiting cell adhesion molecules.110 One case report describes a patient treated with pegIFN-α2a and RBV while on methotrexate for rheumatoid arthritis.111 SVR was achieved but cytopenias (nadir white blood cell (WBC) count of 1.8, platelet (PLT) count of 68,000) and a rheumatoid arthritis flare required the methotrexate dose to be decreased and then increased. After completion of the patient’s antiviral

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**Table 9. Antimetabolites**

| Study | Type | n | Age | Male, % | Reason for IS | AT | PegIfNa-2a + RBV | Adverse Effects |
|-------|------|---|-----|--------|--------------|----|----------------|----------------|
| Noguchi, 2011 | Case report | 1 | 39 | 0% | RA | Methotrexate + bucillamine | PegIfNa-2b + RBV | MTX decreased 2/2 leukopenia (1.8) and thrombocytopenia (68,000). MTX then increased 2/2 RA flare |
| Wan, 2009 | Case report | 1 | 54 | 100% | AIH + HCV | Azathioprine + prednisone taper | PegIfNa-2b switched to PEG-IFN on day 7 | No SVR. HCV VL always detectable. AIH in clinical remission |
| Peyrin-Biroulet, 2008 | Case series | 8 | 47 | 63% | IBD | Azathioprine | PegIfNa-2b + RBV | MTX decreased 2/8, EPO in 7/8, G-CSF in 5/8, RBV discontinue |
| Scherzer, 2008 | Case series | 3 | 47 | 67% | Crohn’s | Azathioprine | PegIfNa-2a + RBV | SVR, HR, increased CD activity in 2/3 (required steroids) |
| Study                | Type            | n  | Age | Male, % | Reason for IS | Immunosuppression                             | AT                        | Outcomes          | Adverse Effects                                                                 | SVR, % |
|---------------------|-----------------|----|-----|---------|--------------|-----------------------------------------------|---------------------------|-------------------|---------------------------------------------------------------------------------|--------|
| Hahn, 2015          | Case series     | 1  | 50  | 100%    | RA           | Hydroxychloroquine, methylprednisolone 8 mg QD, | Sofosbuvir/ledipasvir/GS-9451 × 6 wks | SVR24            | RA flare after completion of AT                                                  | 100%   |
| Mitoro, 1993        | Case report     | 1  | 34  | 100%    | UC           | Sulfasalazine for treatment of UC flare that followed initiation of IFN-α | IFN-α × ~2.5 mo. Restarted 1 wk after sulfasalazine was started | ALT decreased but not normalized | Initial administration of IFN-α caused a flare of UC. There was no recurrence after IS was started |        |
| Allen, 2013         | Case series     | 7  | 53  | 56%     | IBD          | Mesalamine (+ azathioprine in 2/7 pts)          | IFN + RBV × 3–12 mo       | SVR in 4/7 (2/2 on mesalamine and AZA; 2/5 on mesalamine alone) | IBD flare in 1/7 patients. No treatment stopped because of cytopenia | 67%    |
| Alok, 2010          | Case report     | 1  | 58  | 100%    | Crohn’s      | Mesalamine                                     | PegIFN-α2a + RBV          | SVR. Bowel symptoms exacerbated | Budesonide given for IBD flare 13 wks into AT. Loperamide given for worsening IBD symptoms (CRP wnl) 8 mo into AT. Anemia requiring reduction of ribavirin | 100%   |
| Scherzer, 2008      | Case series     | 4  | 54  | 50%     | Crohn’s      | Mesalamine                                     | PegIFN-α2a + RBV × 48 wks | SVR in 2/4. Relapse in 2/4 (required steroids + ABX + mesalamine; steroids; and mesalamine) | Increased CD activity in 3/4 | 50%    |

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Table 11. Other immunosuppressive agents

| Study          | Type                      | n  | Age | Male, % | Reason for IS | Immunosuppression | AT                          | Outcomes                      | Adverse Effects                                                                 | SVR, % |
|----------------|---------------------------|----|-----|---------|---------------|-------------------|------------------------|--------------------------------|--------------------------------------------------------------------------------|--------|
| Agha, 2013     | Prospective interventional study | 8  | 30  | 63%     | SSD           | Hydroxyurea       | PegIFN-α2a + RBV      | SVR: 6/8 SSD: overall decrease in median transfusion and pain crises     | "Well-tolerated" and "without relevant side effects." All completed the study | 75     |
| Azhar, 2010    | Case report               | 1  | 40  | 0%      | AIH + HCV     | MMF               | Consensus IFN + RBV  | SVR Achieved. No hepatitis flares                                     | Cytopenias requiring filgrastim and EPO | 100    |
| Scherzer, 2008 | Case series               | 1  | 56  | 100%    | Crohn's       | MMF               | PegIFN-α2a + RBV × 48 wks | SVR                            | Increased CD activity requiring dilation of stenosis                        | 100    |
| Cornberg, 2002 | Prospective cohort        | 38 | 45  | 79%     | HCV (trial)   | MMF × 24 wks      | IFN-α2a × 24 wks     | Study discontinued due to inefficacy. After 12 wks of therapy, only 1/29 had negative HCV | No serious AEs. No signs of diminished liver function. Not worse than IFN-α monotherapy |        |

1 Median

Table 12. Direct-acting agents with interferon

| Study          | Type                      | n  | Age | Male, % | Reason for IS                                           | Immunosuppression     | AT                          | Outcomes                                                                 | Adverse Effects                                                                 | SVR, % |
|----------------|---------------------------|----|-----|---------|---------------------------------------------------------|-----------------------|------------------------|--------------------------------|--------------------------------------------------------------------------------|--------|
| Saadoun, 2014  | Prospective cohort        | 4  | N/A | N/A     | Mixed cryoglobulinemia vasculitis                       | Rituximab given 1 mo before AT | PegIFN-α + RBV × 48 wks + telaprevir × 12 wks or boceprevir × 44 wks | PR in 2/4 and CR in 2/4                                                                 | Not reported separately                                                                 |        |
| Humphries, 2014| Case report               | 1  | 59  | 100%    | Type II cryoglobulinemia (manifesting as MPGN and skin ulcers) | Methylprednisolone 500 mg × 2d and plasmapheresis × 5 | IFN, RBV, telaprevir × 24 wks | PR. Progressed to ESRD on HD 7 wks after end of tx. SVR achieved | Anemia requiring transfusions, EPO, and interruption of IFN and RBV | 100    |
| Study           | Type                  | n  | Age | Male, % | Reason for IS | Immunosuppression Description                                                                 | AT                          | Outcomes                                                                 | Adverse Effects | SVR, % |
|-----------------|-----------------------|----|-----|---------|---------------|-------------------------------------------------------------------------------------------------|-----------------------------|--------------------------------------------------------------------------|----------------|---------|
| Basu, 2016⁶⁶    | Randomized controlled trial | 35 | 50  | 74%     | IBD           | TNF-α antagonists maintained for the entire duration of AT                                         | LDV + SOF + RBV 1000 mg × 8 wks or LDV + SOF × 12 wks | SVR12 in 34/35 (100% study retention)                                   | Hb < 8.5 in 2. Severities of other AEs are unclear | 97%     |
| Sise, 2016⁷⁶    | Case series           | 5  | N/A | N/A     | Mixed cryoglobulinemia | Rituximab × 4 pts Ustekinumab × 1 pt                                                               | Sofosbuvir + ribavirin or sofosbuvir + simeprevir × 12 wks | SVR12 in 3/4 pts on rituximab and 0/1 pts on ustekinumab (relapsed) | Not reported separately | 60%     |
| Hahn, 2015¹¹⁵   | Case series           | 1  | 50  | 100%    | Rheumatoid arthritis | Hydroxychloroquine, methylprednisolone 8 mg QD, sulfasalazine                                     | sofosbuvir/ledipasvir/GS-9451 ×6 wks | SVR24                                                                    | RA flare 1 wk after completion of AT                                  | 100%    |
| Davar, 2015⁹⁴   | Case report           | 1  | 59  | 0%      | Advanced melanoma | Pembrolizumab ×15 cycles                                                                          | Ledipasvir + Sofosbuvir started after cycle 9 of pembrolizumab | Melanoma: “excellent PR.” Undetectable HCV VL and normal ALT and AST after 6 additional cycles of pembrolizumab | None reported                                                     |         |
therapy, she was started on a prednisolone taper and adalimumab for worsening rheumatological symptoms.

Few conclusions can be drawn from this limited evidence base, but these cases demonstrate that SVR is feasible with IFN-based regimens, although their use may be limited by adverse effects. Data supporting the use of all-oral regimens in patients undergoing antimetabolite therapy are needed to support recommendations in this population.

5-Aminosalicylic Acid (ASA) Derivatives

Like azathioprine, the 5-ASA derivatives sulfasalazine and mesalamine are used to reduce inflammation in IBD and various autoimmune diseases, often in combination with other immunosuppressive agents. In the four studies that examined their use in patients with IBD who were undergoing IFN-based antiviral regimens, SVR was achieved in 7 of 12 patients (Table 10). 107,112–114 Two of the 12 patients were also on methotrexate, both achieved SVR. One case report describes a new diagnosis of ulcerative colitis due to a flare that closely followed initiation of IFN-based antiviral therapy. 112 SVR was not reported. Increased IBD activity during concomitant antiviral and immunosuppressive therapy was observed in 5 of 13 total patients. Severity of the IBD flares was variable; one patient required steroids, mesalamine and antibiotics, while another patient required budesonide.

In the setting of IBD, IFN-based antiviral therapy appears equally effective at achieving SVR. The frequency of IBD flares does seem high given that 5-ASA derivatives are typically equally effective at achieving SVR. The frequency of IBD flares requiring increased immunosuppression 104,107,111,114,115 was reported. Adverse effects included one patient with a flare of rheumatoid arthritis and two patients with anemia (hemoglobin, 8.5). One study describes a patient treated with ledipasvir and sofosbuvir while receiving immunosuppressive therapy for advanced melanoma; 84 SVR was not reported. In general, it appears that all-oral regimens can be very effective even when patients are on immunosuppressive medications. More data in larger cohorts are needed to strengthen the evidence base for the use of all-oral DAAs in patients undergoing immunosuppressive drug therapy; although this will likely represent a preferred strategy for treatment over IFN-based regimens, which have been associated with autoimmune disease flares requiring increased immunosuppression 104,107,111,114,115 and serious adverse events, including death. 71,105,108

Other Immunosuppressive Agents

A number of studies report antiviral therapy used in the setting of immunosuppressant regimens that do not fit adequately within the groups above (Table 11). One single-armed interventional study of pegIFN–α2a and RBV in patients with scleroderma disease on hydroxyurea achieved SVR in 6 of 8 total patients, while transfusions and pain crises decreased. 116 Adverse effects were not described in detail.

Three studies described mycophenolic acid administered concomitantly with IFN. The largest of these was a single-armed prospective interventional trial of a 24-week course of mycophenolic acid and IFN–α2a for the treatment of chronic HCV infection in 38 previous non-responders. 117 The study was discontinued after an interim analysis at 12 weeks found that only 1 of 29 patients assessed at that point had undetectable VL. No patients experienced serious adverse effects or diminished hepatic function. In a case report of mycophenolic acid administered concomitantly with consensus IFN and RBV to a patient with AIH and HCV infection, SVR was achieved. 118 No hepatitis flares were observed but the patient did require filgrastim and EPO. In another study, a patient on mycophenolic acid for Crohn’s disease was treated with pegIFN–α2a and RBV. 107 SVR was achieved but the patient experienced increased IBD activity and required dilation of a stenotic region of bowel. Taken together, these studies show that IFN-based antiviral therapy can cause a range of side effects in patients on mycophenolate mofetil. Furthermore, as in the studies of cytotoxic chemotherapy applied as an adjunct to IFN for the treatment of HCV, adding mycophenolate mofetil does not increase effectiveness.

DAAs

The majority of the studies in this review examine the use of historical IFN-containing regimens. However, DAAs have supplanted these regimens for the treatment of chronic HCV infection.

Two studies investigate the use of historical regimens of telaprevir or boceprevir in combination with IFN (Table 12). In four patients who had received rituximab 1 month prior for the treatment of mixed cryoglobulinemia, SVR was not reported and adverse effects were not reported separately for these patients from the larger study population in either study. 72 In a patient undergoing plasmapheresis and 2 days of high-dose methylprednisolone for MPGN and skin ulcers secondary to cryoglobulinemia, SVR was achieved but renal dysfunction progressed to end-stage renal disease and severe anemia required transfusions, erythropoietin and interruption of IFN and RBV. 74

Four studies examined the use of all-oral regimens in 42 patients who were on an array of immunosuppressive agents (Table 13). 66,76,94,115 SVR was achieved in 38 of 41 patients (92.6%) reportedly. Adverse effects included one patient with a flare of rheumatoid arthritis and two patients with anemia (hemoglobin, 8.5). One study describes a patient treated with ledipasvir and sofosbuvir while receiving immunotherapy for advanced melanoma; 94 SVR was not reported. In general, it appears that all-oral regimens may be very effective even when patients are on immunosuppressive medications.

More data in larger cohorts are needed to strengthen the evidence base for the use of all-oral DAAs in patients undergoing immunosuppressive drug therapy; although this will likely represent a preferred strategy for treatment over IFN-based regimens, which have been associated with autoimmune disease flares requiring increased immunosuppression 104,107,111,114,115 and serious adverse events, including death. 71,105,108

Discussion

Hepatitis C is the most common chronic bloodborne infection in the United States. 119 In those with acute HCV infection, approximately 80% will develop chronic hepatitis C. 120 Untreated chronic infection can lead to liver fibrosis, cirrhosis, HCC, liver failure and need for liver transplant. Extra-hepatic complications include type-1 MPGN, cryoglobulinemia and vasculitis. The development of all-oral DAA regimens, which are more effective and more tolerable than IFN-based regimens, provide clinicians with the opportunity to prevent these negative outcomes in patients who are unsuitable for IFN-based therapy. Concomitant administration of immunosuppressive therapy may at first seem antithetical to the rationale
behind IFN-based regimens; however, a growing body of evidence has been reported that supports their efficacy and safety. Trials of antiviral therapy in patients coinfected with HIV and HCV or on immunosuppressive therapy for solid organ transplant have demonstrated that treating HCV in immunocompromised patients can be effective at achieving SVR, albeit at lower rates than in patients with intact immune systems.1–3

While virologic relapse after SVR was seldom reported in the studies we examined, experience from coinfected patients also shows that recurrence of HCV after achieving SVR is rare. A recent systematic review of non-transplant patients who were treated and achieved SVR in the IFN era revealed a 5-year risk of recurrence of 15%, as compared to the 0.95% reported among monoinfected patients without a recognized risk factor (injection drug use, men who have sex with men or imprisonment) and the 10.67% reported among their subjects exclusively from populations with recognized risk factors (men who have sex with men and incarcerated patients). Indeed, all cases of recurrence were confirmed to be reinfection rather than late relapse. A separate study of six patients with lupus treated with pegIFN and RBV reported late relapse in two patients.1

The key limitation to the development of guideline statements addressing HCV treatment in patients undergoing immunosuppressive drug therapy is the poor quality of evidence, with a predominance of retrospective cohorts and case series; only eight prospective interventional trials evaluating 185 patients were identified in this systematic review. Available data strongly suggest that all-oral DAA regimens are well tolerated and associated with similar rates of SVR as those reported in patients without immunosuppression, and are unlikely to precipitate autoimmune disease activity.1–4

Conclusion

Patients on immunosuppressive therapy represent a neglected population that may stand to benefit from advances in antiviral therapy for HCV infection. While IFN-based regimens can be safe and effective in some settings, side effects are significant and efficacy is far from perfect. Furthermore, evidence is lacking in key areas, such as patients with cancer. DAA therapies have potential to greatly increase the number of patients treated for HCV, but there is scant data on the use of these agents in immunosuppressed patients outside of the transplant setting. Adequately powered studies, ideally prospective observational cohort or multicenter randomized controlled trials, are needed to further strengthen the evidence base to inform guidelines on optimal all-oral treatment regimens for patients with HCV who are undergoing immunosuppressive drug therapy.

Conflict of interest

None

Author contributions

Drafting of the manuscript (KO), contributing to the conception and design (KO, JKL), contributing to critical revisions of the manuscript (JKL).

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