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Secukinumab in the Treatment of Psoriasis and Psoriatic Arthritis: A Review of the Literature

Michael Abrouk, MD[1]; Jessica Gandy, MD[1]; Mio Nakamura, MD[2]; Kristina Lee, MS[2]; Merrick Brodsky, MD[1]; Rasnik Singh, MD[3]; Henry Zhu, MD[4]; Benjamin Farahnik, MD[5]; Tina Bhutani, MD[2]; John Koo, MD[2]

[1]Irvine School of Medicine, University of California, CA, USA

[2]Department of Dermatology, Psoriasis and Skin Treatment Center, University of California - San Francisco, San Francisco, CA, USA

[3]David Geffen School of Medicine, University of California - Los Angeles, Los Angeles, CA, USA

[4]Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

[5]The Larner College of Medicine, University of Vermont, Burlington, VT, USA

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ABSTRACT

While there are several commercially available treatment options for psoriasis and psoriatic arthritis, there remains a large number of individuals who are refractory to current modalities. In the recent past, there has been increasing evidence that interleukin (IL)-17 plays a vital role in the pathophysiology of psoriasis. Preclinical, phase II, and phase III studies of secukinumab (Cosentyx®) targeting IL-17 and its receptor have thus far proved to be promising. We reviewed the results of phase II and phase III clinical trials for secukinumab in the treatment of psoriasis and psoriatic arthritis. Only published studies were considered in the present review. We also performed an English language literature search from January 2003 to September 2015 using PubMed with any of the following key words: (secukinumab OR AIN457) AND (psoriasis OR psoriatic arthritis). In our review of the literature, seven phase III and five phase II clinical trials, as well as open-label extension studies with unpublished findings were found. Results from phase III clinical trials indicated secukinumab to be efficacious and safe for the treatment of psoriasis and psoriatic arthritis according to Psoriasis Area and Severity Index (PASI) and American College of Rheumatology (ACR) scores. The safety profile of this agent was similar across all studies, with the most frequently reported adverse events of nasopharyngitis, upper respiratory infections, headache, and injection site reaction. Secukinumab demonstrates rapid and robust clinical improvement accompanied by a favorable short-term safety profile. The results of the phase III trials continue to reinforce the theory that the IL-17 pathway is an essential target in psoriasis and psoriatic arthritis treatment. Additional extension studies of lower level evidence are needed to further understand the safety profile of the drug.

Key words: anti-interleukin-17, biologics, IL-17A, psoriasis, psoriatic arthritis, secukinumab, therapy

Introduction

Psoriasis is a common, multifaceted chronic inflammatory disease of the skin that affects 3-4% of the adult population in the United States, with 5-30% suffering from concurrent psoriatic arthritis.[1,2] The pathogenesis is largely multifactorial with a combination of immune dysregulation, genetic susceptibility, and environmental factors; thus, there is a wide range of disease severity and areas of involvement. While there are a number of available treatment options currently on the market, there are still many individuals who remain refractory to these modalities.

Since there still remains a large population of individuals who are resistant to current treatment methods, the need for further research to develop novel therapeutic modalities is great.[3,4] The interleukin (IL)-17 pathway has demonstrated significant potential as a new target for treatment. As a proinflammatory cytokine, IL-17 is produced by type 17 helper (Th-17) T cells and is a downstream product of IL-23.[5-8] The IL-17 pathway mediates a diverse set of biological responses that contribute to the eventual inflammation, activation and recruitment of neutrophils, cessation of neutrophil apoptosis, and angiogenesis.[9-12] There has also been increasing research of IL-17, including the the IL-17 receptor, and its expression in synovial tissues, as well as its importance in the pathogenesis of psoriatic arthritis.[13-15] To futher support the role of IL-17 in psoriatic disease, studies have

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demonstrated elevated levels of IL-17 in both the serum and lesions of patients with active psoriasis.[16-21]

One of the newest biologic agents approved by the US FDA for the treatment of psoriasis is secukinumab (Cosentyx®), a fully human monoclonal antibody. Secukinumab acts by inhibiting the effector function of IL-17A and has been shown in previous studies to be better than placebo and etanercept.[22] Herein, we review the data regarding the efficacy and safety of secukinumab in patients with moderate-to-severe plaque psoriasis.

Mechanism of Action and Pharmacokinetics

Secukinumab is a human immunoglobulin G1 kappa (IgG1k) monoclonal antibody that binds and neutralizes IL-17A. IL-23 activates Th-17 cells, which release IL-17.[23] IL-17 release increases expression of proinflammatory cytokines leading to recruitment of immune cells, activation of keratinocytes, and enhancement of angiogenesis. This can eventually lead to synovial inflammation and psoriatic plaque development.[23] Secukinumab has been administered either subcutaneously (SC) at a low, medium or high dose (75 mg, 150 mg, 300 mg) or intravenously (IV) at a dose of 10 mg/kg.[24] Secukinumab is available in 150 mg pre-filled syringes or injection pens. The FDA approved dosing for the treatment of psoriasis with secukinumab consists of SC injections with a loading dose of once weekly 300 mg injections for the first 4 weeks for induction, followed by 300 mg every 4 weeks thereafter for maintenance. A dose of 150 mg was acceptable for some patients.[23] For patients being treated for psoriatic arthritis, the dosing schedule is as follows: secukinumab is administered with a SC injection of 150 mg every week for the first 4 weeks as a loading dose, followed by 150 mg every 4 weeks thereafter. For patients with both psoriasis and psoriatic arthritis, the psoriasis dosing is recommended. Maximal plasma concentration is reached in approximately 6 days and the mean half-life is 27 days with an average bioavailability of 73%. Typically, secukinumab takes the form of a lyophilized formulation that can be reconstituted.[23] However, two clinical trials, FIXTURE and JUNCTURE, have detailed the various preparations and dosing forms of secukinumab, which includes a liquid formulation delivered either via pre-filled syringe or an auto-injector pen, respectively.[22,25]

Methods

We reviewed the results of clinical trials for secukinumab in the treatment of psoriasis and psoriatic arthritis. Only completed studies were considered in the present review; recruiting, not yet recruiting, withdrawn and terminated trials were eliminated (Table 1). In order to identify any other studies that may have assessed secukinumab, we performed an English language literature search from January 2003 to September 2015 using PubMed with any of the following key words: (secukinumab

Trial	First Author	Comparator	N	Dosing
JUNCTURE	Paul	Placebo	404	Secukinumab 150 mg SC single administration at week 0, or 150 mg SC at weeks 0, 1, 2, 4, or 150 mg SC at weeks 0, 4, 8, or placebo
FEATURE	Blauvelt	Placebo	177	Secukinumab 150 mg or 300 mg SC once weekly between weeks 0 and 4, and once again at week 8, or placebo
ERASURE	Langley	Placebo	738	Secukinumab 150 mg or 300 mg SC once weekly for 5 weeks then every 4 weeks, or placebo
FIXTURE	Langley	Etanercept	1306	Secukinumab 150 mg or 300 mg SC once weekly for 5 weeks then every 4 weeks, or etanercept SC twice weekly for 12 weeks then once weekly, or placebo
ERASURE subanalysis	Ohtsuki	Placebo	87	Secukinumab 150 mg or 300 mg SC once weekly for 5 weeks then every 4 weeks, or placebo
SCULPTURE	Mrowietz	Placebo	966	Secukinumab 150 mg or 300 mg SC weekly for 5 weeks then once at week 8, then at week 12 patients achieving PASI75 were re-randomized to either 150 mg or 300 mg SC given at fixed interval or retreatment as-needed regimen
STATURE	Thaci	Placebo	43	Secukinumab 10 mg/kg IV at baseline, weeks 2 and 4, or 300 mg SC at baseline and week 4
CLEAR	Thaci	Ustekinumab	676	Secukinumab 300 mg SC at weeks 0, 1, 2, 3, and every 4 weeks starting at week 4, or ustekinumab 45 mg or 90 mg SC (depending on subject body weight at baseline) at weeks 0 and 4 and then every 12 weeks
FUTURE 1	Mease	Placebo	606	All patients assigned to receive an IV loading dose of secukinumab at a dose of 10 mg/kg at 0, 2, and 4 weeks followed by secukinumab SC at a dose of either 150 mg or 75 mg every 4 weeks or placebo. Placebo group was switched to secukinumab SC at a dose of 150 mg or 75 mg at week 16 or 24 depending on the clinical response.
FUTURE 2	McInnes	Placebo	397	Secukinumab 300 mg or 150 mg or 75 mg SC to receive once a week from baseline and then every 4 weeks from week 4

Table 1: Phase III clinical trial data for secukinumab

OR AIN457) AND (psoriasis OR psoriatic arthritis). We also reviewed citations within articles to identify relevant resources. Overall measures of efficacy and incidence of adverse events for each medication were calculated by tabulating values from independently conducted studies (Table 2). To the best of our knowledge there was only one open label extension study and no studies of lower level of evidence (3, 4, or 5), such as case series or case reports, commenting on the efficacy or side effects of secukinumab on a smaller scale.[26]

Clinical Trials

Phase I/II Trials

In the recent past, a few phase I and II trials have been published investigating the overall safety, tolerability, and initial response of secukinumab on psoriatic lesions. There were two phase I trials conducted exploring the distribution of secukinumab into dermal interstitial fluid after SC administration of 300 mg. In total, there were five phase II trials determining the dosing regimen and effect of secukinumab treatment, as well as skin response of psoriasis patients. In one of these phase II trials, Papp et al. investigated the overall efficacy of secukinumab in treating moderate-to-severe plaque psoriasis.[27] After 12 weeks of treatment, secukinumab resulted in significantly higher Psoriasis Area and Severity Index (PASI) scores with at least 75% improvement from baseline (PASI75) vs. placebo at 3 times 75 mg and 3 times 150 g SC doses. In another phase II trial by McInnes et al., secukinumab was found to significantly improve quality of life and acute phase reactant levels vs. placebo, as well as overall satisfactory safety scores.[28] Rich et al. demonstrated the efficacious effects of secukinumab for induction and maintenance of treatment in patients with moderate-to-severe plaque psoriasis in their phase II randomized control trial.[29] Finally, studies by Sigurgeirsson et al. and Paul et al. demonstrated efficacy of secukinumab for psoriatic lesions on the extremities and nail lesions, respectively.[30,31]

Phase III Trials

Seven phase III clinical trials have been completed to determine the efficacy and safety of different doses of secukinumab for plaque psoriasis and psoriatic arthritis.[24,28,31-35] The most recent trials, FUTURE 1 and FUTURE 2, essentially validated IL-17A as a therapeutic target for the treatment of psoriasis and psoriatic arthritis. In the FUTURE 2 phase III, double-blind, placebo-controlled study, patients receiving the 300 mg, 150 mg and 75 mg doses were found to achieve a significantly higher American College of Rheumatology (ACR20) score at week 24 compared with placebo. The most common adverse events reported were urinary tract infections and nasopharyngitis.[31] FUTURE 2 is the first large phase III trial for secukinumab. Data from week 52 suggests that the efficacy of the drug at higher dosages (300 mg and 150 mg) can be sustained over long periods of time.[28] In FUTURE 1, another randomized, double-blind phase III trial, the efficacy of IV secukinumab (10 mg/kg) followed by SC dosing vs. placebo was evaluated. In this study, patients with psoriatic arthritis received IV secukinumab at weeks 0, 2, and 4 followed by either placebo or a SC dose of either 150 mg or 75 mg every 4 weeks. The primary endpoint was a 20% improvement from baseline in the ACR20 by week 24. ACR20 scores at week 24 were significantly higher in the group receiving the SC secukinumab vs. the IV dosing paired with placebo. The most common adverse events were nasopharyngitis, headache, upper respiratory tract infection, and diarrhea. Serious adverse events included stroke (4), myocardial infarction (2) vs. no serious adverse events (AEs) in the placebo group.[24]

ERASURE, a two-phase III double-blind, 52-week trial used the PASI75 to compare secukinumab to placebo. Langley et al. demonstrated that secukinumab at 300 mg and 150 mg SC was significantly superior in treating psoriasis compared to placebo. This trial showed that the 300 mg and 150 mg SC doses of secukinumab were markedly more effective in treating psoriasis than etanercept. In an ERASURE 52-week subanalysis published by Ohtsuki et al., secukinumab was found to be efficacious in the long-term treatment of plaque psoriasis in Japanese patients.[22,36]

In a different study with a similar design by Langley et al., the FIXTURE trial compared secukinumab to placebo and etanercept. This trial showed that secukinumab 300 mg was superior to etanercept 50 mg twice weekly in terms of proportion of patients reaching PASI75 (77.1% vs. 44%, respectively) and PASI90 (54.2% vs. 20.7%, respectively) ($P<0.001$ for all groups compared to placebo).[22]

FEATURE and JUNCTURE each compared the efficacy of secukinumab to placebo when administered by pre-filled syringe (FEATURE) and auto-injector pen (JUNCTURE). Both studies by Blauvelt et al. and Paul et al., respectively, demonstrated that secukinumab administration via either syringe or injector pen was effective with acceptable safety profiles.[25,33,34]

The CLEAR trial compared secukinumab to ustekinumab, demonstrating secukinumab 300 mg was more efficacious than ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg) in terms of proportion of patients achieving PASI75 (91% vs. 79.1%, respectively) and investigator's global assessment (IGA) of 0 or 1 (80.8% vs. 65.1%, respectively). The SCULPTURE trial investigated the retreatment as-needed protocol vs. fixed interval regimen of secukinumab dosing. At week 12, patient outcomes were assessed with the PASI75, at which point participants were re-randomized to two new groups: retreatment as-needed or fixed interval dosings. The primary endpoint was maintaining PASI75 results until week 52. Mroweitz et al. demonstrated that secukinumab at fixed interval dosing (every 4 weeks after the initial loading dose) conferred clear benefit vs. the retreatment as-needed model. Both protocols showed that AEs were comparable to other trials with no serious AEs noted. Although both protocols require further study.[25,33,34]

By week 12, the five studies comparing secukinumab to placebo each demonstrated statistically significant superiority of secukinumab over placebo at all SC dosings. Within these studies, the proportion of patients reaching PASI75 was statistically significant for all dosing levels of secukinumab (300 mg, 150 mg, and 75 mg) vs. comparators and placebo. Secukinumab was similarly superior to placebo in terms of IGA 0/1, ACR20, ACR50, PASI90, PASI100, and the Dermatology Life Quality Index (DLQI) (Table 2). The most common AEs among the studies were nasopharyngitis, headache, upper respiratory tract infection, and diarrhea. Mild and transient neutropenia, without associated infections, was noted in a minority of patients in each trial. Some serious adverse effects observed in the FUTURE 1 trials were stroke and myocardial infarction (Table 1).

Endpoint	Study	Secukinumab 300 mg	Secukinumab 150 mg	Secukinumab 75 mg	Placebo	Etanercept 50 mg	Ustekinumab 45 mg or 90 mg
PASI75	ERASURE	81.6%†	71.6%†	––	4.5%	––	––
	FIXTURE	77.1%†*	67%†*	––	4.9%	44%	––
	FEATURE	75.9%‡	69.5%‡	––	0%	––	––
	JUNCTURE	86.7%‡	71.7%‡	––	3.3%	––	––
	CLEAR	91%¢	––	––	––	––	79.1%
	FUTURE 1	––	61.1%*	64.8%*	8.3%	––	––
	FUTURE 2	63%‡	48%‡	28%‡	16%	––	––
	SCULPTURE	By week 12: 90.1% Fixed interval: 84.4% week 52: 59.7% Retreatment as needed: 67.6% week 52: 13.8%	By week 12: 84.4% Fixed interval: 62.1% week 52: 45.8% Retreatment as needed: 52.4% week 52: 11.2%	––	––	––	––
PASI90	ERASURE	59.2%†	39.1%†	––	1.2%	––	––
	FIXTURE	54.2%†*	41.9%†*	––	1.5%	20.7%	––
	FEATURE	60.3%‡	45.8%‡	––	0%	––	––
	JUNCTURE	55%‡	40%‡	––	0%	––	––
	CLEAR	72.8%¢	––	––	––	––	53.4%
	FUTURE 1	––	45.3%*	49%*	3.6%	––	––
	FUTURE 2	49%**	33%**	12%**	9%	––	––
PASI100	ERASURE	28.6%†	12.8%†	––	0.8%	––	––
	FIXTURE	24.1%|*	14.4%|*	––	0%	4.3%	––
	FEATURE	43.1%‡	8.5%¤	––	0%	––	––
	JUNCTURE	26.7%‡	16.7%¶	––	0%	––	––
	CLEAR	8.9%¥	––	––	––	––	25.7%
IGA 0/1	ERASURE	65.3%†	51.2%†	––	2.4%	––	––
	FIXTURE	62.5%†*	51.1%†*	––	2.8%	27.2%	––
	FEATURE	69%‡	52.5%‡	––	0%	––	––
	JUNCTURE	73.3%‡	53.3%‡	––	0%	––	––
	CLEAR	80.8%¢	––	––	––	––	65.1%
ACR50	FUTURE 1	––	34.6%*	30.6%*	7.4%	––	––
	FUTURE 2	35%‡‡	35%‡‡	18%‡‡	7%	––	––
ACR20	FUTURE 1	––	50%*	50.4%*	17.3%	––	––
	FUTURE 2	54%‡	51%‡	29%‡	15%‡	––	––

Table 2: Primary and secondary endpoints at week 12 for secukinumab compared to placebo, etanercept, and ustekinumab

Disclaimer: These data were tabulated from independent studies that were not conducted in a head-to-head manner.

PASI: Psoriasis Area and Severity Index; values indicate percentage improvement of cutaneous symptoms

IGA: Investigator's global assessment

†P<0.001 for the comparison with placebo

| No comparison with placebo was performed because there were no patients with a response in the placebo group

*P<0.001 for the comparison with etanercept

**P<0.0005 for the comparison with placebo

‡P<0.0001 for the comparison with placebo

¤P=0.057 for the comparison with placebo

‡‡P=0.057 for the comparison with placebo

¶P=0.0006 for the comparison with placebo

¢P<0.0001 for the comparison with ustekinumab

¥P=0.0003 for the comparison with ustekinumab

Cost-Utility of Secukinumab

Currently, there have been only a few studies detailing the cost-benefit analysis of secukinumab for moderate-to-severe plaque psoriasis. Lee et al. evaluated the cost utility of secukinumab, as well as other systemic biologic agents, compared with the standard of care, which was arbitrarily defined as methotrexate, cyclosporine, topical corticosteroids, or phototherapy.[37] The investigators demonstrated that secukinumab was associated with the second highest total cost ($70,313 Canadian dollars). The lowest cost was the standard of care. However, the highest quality of life (QoL) gains were found with secukinumab 300 mg. Thus, while the standard of care with non-biologics remains the most appropriate option in terms of cost analysis, Lee et al. posits that biologic agents, especially secukinumab, yield substantial QoL gains. Since psoriasis and psoriatic arthritis can be debilitating conditions in terms of their impact on QoL, productivity loss, psychosocial issues and individual burden of disease, biological agents such as secukinumab have the potential to replace the standard of care due to marked improvements in QoL.[15,18-20,23,29,32-34,38-44]

Discussion

Secukinumab has the potential to address the unmet needs of patients with psoriasis refractory to current treatment modalities. The results of phase III clinical trials reinforce IL-17 as an essential therapeutic target and demonstrate the overall efficacy of secukinumab in the treatment of psoriasis and psoriatic arthritis. In the treatment of psoriasis, secukinumab was found to perform significantly better than several contemporary biologic agents currently in use, such as etanercept and ustekinumab. Within the context of these studies, there were no substantial differences noted in the safety profiles of secukinumab compared with other biologic agents; the most common AEs included nasopharyngitis, upper respiratory infection, and headache. However, there were several other AEs that were unique to secukinumab and not observed with etanercept, adalimumab, or ustekinumab. Some of the AEs unique to secukinumab were neutropenia, diarrhea and candidiasis, but was thought to be IL-17 specific. A small portion of patients experienced low-grade neutropenia with each of the agents, though these episodes were self-controlled and transient. Mild or moderate *Candida* infections were more frequent with secukinumab compared with etanercept, ustekinumab, and placebo. No patients discontinued the study drug due to *Candida* infections and no serious or invasive fungal infections were reported in any of the studies.

Recent epidemiologic studies suggest that treating psoriasis with systemic immunosuppressant therapies leads to a reduction of cardiovascular events such as myocardial infarction and stroke. Interestingly, IL-17 has been measured in atherosclerotic plaques and thought to play an important role in overall plaque formation. Past studies have reported elevated levels of IL-17 in patients suffering from unstable angina and acute myocardial infarction. In tandem, these findings suggest that blocking the IL-17 pathway through biologic agents, such as secukinumab, has the potential to reduce the overall risk of cardiovascular events in patients with psoriasis. However, we do not yet have any long-term data for this medication, unlike the long-term safety and efficacy data available for other biologics like etanercept and adalimumab. While the initial clinical results reviewed here look promising, more long-term data is needed for secukinumab.[15,18-20,23,29,32-34,38-44]

Conclusion

Secukinumab has the potential to address the unmet needs of patients with psoriasis and psoriatic arthritis recalcitrant to current treatment modalities. The phase III clinical trials suggest that anti-IL-17 inhibitors have improved efficacy compared to available biologic agents and placebo. Relative to the standard of care with non-biologic therapies, secukinumab is superior in terms of overall QoL scores. Further long-term studies are necessary to confirm the favorable efficacy and safety profiles of this biologic agent demonstrated in phase III trials.

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Hepatitis B and C Viruses and Biologics

Parbeer Grewal MD, FRCPC, FAAD[1] and Ravina Sanghera, PharmD[2]

[1]Division of Dermatology, University of Alberta, Edmonton, AB, Canada

[2]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, AB, Canada

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ABSTRACT

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are common, worldwide viral illnesses that potentially impact the clinician's ability to manage patients with immunosuppressive medications such as biological therapy. In light of recent literature reviews, patients with HBV and HCV should be referred to a hepatologist or infectious disease expert prior to initiation of biological therapy.

Key words: adalimumab, biologic, etanercept, hepatitis B virus, hepatitis C virus, infliximab, ustekinumab

Introduction

Hepatitis B virus (HBV) is one of the most common, chronic viral illnesses affecting 370 million people worldwide.[1] Most often it is transmitted during birth or early childhood. Reactivated HBV is characterized by an abrupt increase in serum HBV DNA together with increased alanine aminotransferase (ALT) levels.[1] During immunosuppressive therapy, HBV DNA in serum often increases by several log[10] international units (IU), and this can result in activation of HBV-specific effector cells that target and destroy virally infected hepatocytes. This is particularly relevant in psoriatic patient populations because of the higher incidence of underlying fatty liver and alcoholic liver disease. Reactivation of hepatitis B has a wide clinical spectrum, varying from asymptomatic cirrhosis, to liver failure, to hepatocellular carcinoma, and even death in 15-25% of patients. Standard therapy includes antiviral medications such as lamivudine.[1] HBV has always been a relative contraindication to immunosuppressive or biologic therapy.[1] Table 1 summarizes the serological profiles and suggested management of patients with HBV.[1-3]

Hepatitis C virus (HCV) is also one of the most common blood-borne viral infectious diseases affecting 4 million people in the US and 200 million people worldwide.[1] Although 30% of patients can experience spontaneous clearance, 70% of affected individuals will progress to a chronic persistent state of HCV. This ultimately leads to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Standard treatment involves the use of interferon-alpha (IFN-α) and ribavirin, with clearance response rates around 35-45%.[1] Sofosbuvir is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of genotypes 1, 2, 3 or 4 chronic HCV infection as a component of a combination antiviral treatment regimen. Cure rates as high as 95% have been attained following 12 weeks of therapy.[4] However, due to the prohibitively high cost of such medications, many patients will still have to deal with chronic hepatitis C while on immunosuppressive therapy. Biologics, such as etanercept, infliximab and adalimumab, are considered to be relative contraindications and second-line therapies in moderate to severe psoriasis with co-existent HCV.[5] Interestingly, it has been found that tumor necrosis factor (TNF) levels are elevated in HCV, and higher levels of TNF are associated with more inflammation and fibrosis in the liver as well.[6] Table 2 summarizes the Center for Disease Control's (CDC) recommendations regarding the serological profiles and management of HCV.[7]

Discussion

Hepatitis B Virus (HBV)

In a published review of 257 patients treated with anti-TNF agents, there were 42 cases of HBV reactivation reported. This corresponds to a rate of reactivation of 16%, with 80% of cases occurring in hepatitis B surface antigen positive (HBsAg+) carriers, resulting in raised transaminase levels, emerging signs and symptoms of liver disease, the reappearance of serum hepatitis B viral DNA, and a mortality rate of 5%. The authors stated that HBsAg+ carriers with active liver disease and patients presenting with clinical symptoms (e.g., abdominal pain, jaundice, nausea, vomiting, dark urine, pale stools), raised liver enzymes, and/or high viral load should have the HBV infection treated and controlled before initiating therapy. In asymptomatic HBsAg+ carriers, antiviral prophylaxis is recommended and should be started 2-4 weeks prior to anti-TNF therapy and continued for at least 6 months after cessation. In anti-hepatitis B core antibody positive (HBcAB+) persons, routine prophylaxis is not recommended, although individual factors such as the degree of immunosuppression, the length of therapy, and the degree of local HBV endemicity should be taken into account. Regardless, these patients should always be carefully monitored (liver and viral tests every 1-3 months) for the duration of anti-TNF treatment, especially with the use of monoclonal therapy.[8]

In another review conducted between 2007 and 2011, 7 HBV carriers receiving TNF-alpha inhibitors for psoriasis were collected retrospectively. The HBV viral load and aminotransferase levels were regularly monitored. Two of the 7 patients were inactive HBV carriers, and the other 5 patients had chronic hepatitis B. Only 1 patient received antiviral agents before the anti-TNF-alpha treatment. The mean duration of the anti-TNF-alpha treatment was 26.6 months (range, 14-45 months). These patients were followed from the start of the anti-TNF-alpha therapy for a mean duration of 28.9 months (range, 14-45 months). HBV reactivation was observed in 3 patients, 1 of whom required antiviral treatment. No HBV reactivation-related hepatitis was observed.[9]

A separate systemic literature review identified 35 HBsAg+ carriers prior to initiation of TNF-alpha inhibitors. Infliximab was used in 17 cases, etanercept in 12 cases, and adalimumab in 6 cases. All 6 cases of clinically symptomatic hepatitis were associated with infliximab therapy. Infliximab was associated with the most cases of a greater than 2-fold increase in alanine aminotransferase (6 of 9 cases) and greater than 1,000-fold

HBV infection	HBsAg	Anti-HBsAB	Anti-HBcAB	IgM Anti-HBcAB	Abnormal LFTs and/or symptoms	Additional testing	Treatment
Susceptible	–	–	–	–	–	Not necessary	Consider vaccination, treat with biologic
Immune due to natural infection	–	+	+	–	–	Not necessary	Treat with biologic therapy
Immune due to HBV vaccine	–	+	–	–	–	Not necessary	Treat with biologic therapy
Acute infection	+	–	+	+	+	Not necessary	Defer biologic therapy, seek hepatologist
Chronic infection	+	–	+	–	+/–	HBeAg+, HBeAb–, HBV DNA	Treat with biologic in conjunction with hepatologist
4 possibilities: 1. Resolved infection 2. False-positive anti-HBcAB, thus susceptible 3. Low level chronic infection 4. Resolving acute infection	–	–	+	–	+/–	HBeAg–, HBeAB+, HBV DNA	Treat with biologic in consultation with a hepatologist

Table 1: Summary of serological profiles and suggested management of patients with HBV
HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = total Hepatitis B core antibody; IgM anti-HBcAb = IgM to Hepatitis B core antibody; HBeAg = hepatitis B envelope antigen; HBeAB = hepatitis B envelope antibody; LFT = liver function tests.

increase in HBV DNA load (3 of 4 cases). The 2 deaths due to liver failure occurred with infliximab therapy.[10]

In a retrospective analysis of 62 psoriatic patients with occult HBV infection treated with anti-TNF biological agents over a period of approximately 4 years: 44 subjects were treated with etanercept, 8 with infliximab, and 10 with adalimumab. During the observational treatment period, no signs of HBV activation were observed. In 1 patient the reappearance of HBsAg, without detectable HBV-DNA, was noted before retreatment with etanercept and after 10 months from discontinuation of the previous course. In this patient, etanercept was re-administered in association with lamivudine without any adverse event.[11]

Another case report series followed 7 psoriatic arthritis patients with positive HBcAB who were also on adalimumab for 6 years. Only 1 patient was HbSAg+, and this was the only individual started on prophylactic lamivudine. None of the patients experienced reactivation of hepatitis.[12]

A retrospective analysis was done on 17 patients (13 men and 4 women, aged 36-74 years) with plaque-type psoriasis associated with hepatitis infections (11 with past HBV infection, 5 with chronic HCV infection and 1 affected by both HBV and HCV). Fourteen patients had received etanercept, 2 adalimumab and 1 adalimumab as a second biologic treatment after an unsuccessful trial of etanercept. No changes in serum aminotransferases or viral load were reported in any of these cases.[13]

In regards to ustekinumab, there are sporadic case reports available. One patient with chronic HBV was treated with ustekinumab and had no aggravation of hepatitis after 15 months.[6] Another study of 14 patients was conducted where 11 were HBsAg+. Of these patients, 7 were not given antiviral prophylaxis and 2 patients experienced reactivation, whereas the 3 patients with occult HBV infection had no reactivation.[14]

Hepatitis C Virus (HCV)

There are numerous publications that provide evidence supporting the safe use of biological therapy in the context of HCV. A review of 216 patients with HCV exposed to 1 or more TNF-alpha inhibitors over 260 cumulative patient years of exposure revealed only 3 cases of drug withdrawal due to liver issues.[15] In a separate review of 153 patients with HCV infection on TNF-alpha inhibitors, there was only 1 confirmed case of worsening HCV infection.[16] Another retrospective, observational, and multicenter study was carried out in 4 Italian centers. There were 7 patients on adalimumab (40 mg subcutaneously [SC] every 2 weeks) and 8 on etanercept (4 patients at a dosage of 50 mg SC once a week and 4 patients on 25 mg SC twice a week) for a mean of 16 months of therapy (range 12-24 months). During the observation period, these values remained stable and no patients showed reactivation of hepatitis.[17] A prospective open study followed 29 patients with active rheumatoid arthritis that were randomly assigned to receive therapy with methotrexate (MTX) alone, etanercept alone, or a combination of MTX and etanercept, and monitored up to 54 weeks. Aspartate transaminase (AST) and alanine transaminase (ALT) enzyme concentrations did not significantly change in all 3 arms of treatment, nor did the HCV viral load. No patients discontinued the therapy because of worsening liver disease.[18]

Interestingly, Zein et al. conducted a double-blind placebo controlled trial of 50 patients with HCV infection on interferon and ribavirin, and also gave half of the patients concomitant etanercept.[19] The group receiving etanercept actually achieved a higher frequency of viriological and biochemical response and had fewer side effects than the placebo group.[19] A study by Khanna et al. in 2005 reviewed the use of etanercept in 5 clinical studies and also found it to be beneficial when used in combination with standard treatments for HCV.[20]

Test outcome	Interpretation	Further action
HCV antibody nonreactive	No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required. If recent HCV exposure in person tested is suspected, test for HCV RNA.
HCV antibody reactive	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection	Provide person tested with appropriate counseling and link them to medical care and treatment.
HCV antibody reactive, HCV RNA not detected	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In situations involving recent HCV exposure, clinical evidence of HCV or concerns with specimen storage, follow-up with HCV RNA testing and appropriate counseling.

Table 2: Center for Disease Control's recommendations regarding serological profiles and management of HCV[7]

Very few publications, including Orion et al. and Vigna-Perez et al., provide evidence against the use of TNF-α inhibitors in patients with HCV. They found that adalimumab created a down-regulatory effect on T lymphocytes and, thus, indicated an enhanced risk of bacterial tuberculosis or viral infection reactivation.[21,22]

With respect to ustekinumab, 1 small study of 2 patients treated for 15 months had no aggravation or reactivation of HCV.[6] Another publication showed that 2 of 4 patients had an increase in the HCV copy number and 1 patient fulfilled the HCV reactivation criteria and later developed hepatocellular carcinoma.[14]

Conclusion

All patients with HBV should always be referred to a hepatologist or infectious disease expert prior to biological therapy. Almost all of these patients will require prophylactic antiviral therapy. The only possible exceptions might be those recovering from an acute HBV infection with loss of anti-HBc in serum or patients with chronic HBV with seronegative serum profile. If prophylactic therapy is started, an antiviral should be given pre-emptively, either 2 to 4 weeks before or concomitant with the start of immunosuppressive therapy. Lamivudine has been recommended when immunosuppressive therapy is likely to be less than 6 to 12 months, whereas agents with better resistance profiles such as entecavir and tenofovir are considered preferable when immunosuppressive therapy is continued longer.[1] Although curative treatments are available, affordability may prevent access, therefore, we will still have to manage patients with chronic HCV on concomitant biological therapy.

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Update on Drugs

Name/Company	Approval Dates/Comments
Infliximab-abda for IV infusion *Renflexis*® Samsung Bioepis	In April 2017, the US FDA approved infliximab-abda, a biosimilar referencing Remicade® (infliximab, Janssen), across all eligible indications including the treatment of psoriatic arthritis and adult plaque psoriasis.
Ozenoxacin 1% cream *Ozanex*™ Cipher/Ferrer	In May 2017, Health Canada approved ozenoxacin 1% cream, a novel topical antibiotic indicated for the treatment of impetigo in patients aged 2 months and older. It is the first bacteriocidal topical antibiotic that has been shown to be effective against resistant bacteria such as methicillin resistant *Staphylococcus aureus* (MRSA). Ozenoxacin offers a short 5-day twice-daily dosing regimen and has shown bacteriological eradication as early as day 3 of treatment. Ozenoxacin belongs to a new generation of non-fluorinated quinolones that have demonstrated improved tolerability and safety over fluorinated quinolones. Phototoxicity, photoallergenic sensitization and articular toxicity were not observed in local tolerability studies. This drug also demonstrated *in vitro* and *in vivo* antibacterial activity against a broad spectrum of bacteria, including MRSA strains and clinical isolates of organisms with emerging resistance to quinolones and other topical antibiotics.
Standardized allergen extract of house dust mites sublingual tablet *Acarizax*® ALK-Abelló A/S	In May 2017, Health Canada approved this sublingual allergy immunotherapy (SLIT) tablet for the treatment of the signs and symptoms of moderate to severe house dust mite (HDM) allergy. It is formulated as an orally disintegrating tablet designed to rapidly dissolve within seconds under the tongue. The active substance is a standardized allergen extract derived from house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*). Treatment is indicated for adults 18 to 65 years of age with confirmation of positive skin prick test and/or *in vitro* testing for *D. farinae* or *D. pteronyssinus* IgE antibodies. FDA approval was gained in March 2017 and is marketed as Odactra® in the US. Approvals in Europe and Japan under the brand names Acarizax® and Miticure™, respectively, were gained in 2015. In April 2017, Acarizax® had its approval in 12 European countries expanded to include the treatment of adolescent patients with HDM-induced allergic rhinitis.
Doxycycline hyclate immediate release tablet Mayne Pharma Group	In June 2017, the FDA approved the Abbreviated New Drug Application (ANDA) for doxycycline hyclate immediate release (IR) tablets (75 mg and 150 mg). Doxycycline hyclate IR tablets are a generic version of Acticlate® (Aqua Pharmaceuticals), a tetracycline-class antibacterial indicated for the treatment of a number of infections, including adjunctive therapy in severe acne.
Device News	
UVB Phototherapy System *Clarify™ Home Light Therapy System* Clarify Medical	In June 2017, the FDA granted 510(k) market clearance for this mobile handheld, smartphone-connected phototherapy device for treating various skin conditions. Clarify's proprietary technology allows patients with chronic skin diseases, such as psoriasis, vitiligo, and eczema, to receive narrow-band ultraviolet B (UVB) phototherapy in their homes. A prescription from a doctor is required before using the device. The system consists of a physician web portal, smartphone app and treatment device, which are all wirelessly connected, and in combination allows the doctor to be in control of the treatment protocol, but enables the patient to administer the treatment at the time and place they choose.