Budesonide in autoimmune hepatitis: the right drug at the right time for the right patient

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Autoimmune hepatitis (AIH) is a rare liver disease caused by an autoreactive immune response against the patient's own liver. Autoimmune hepatitis may start with an episode of acute hepatitis but usually runs a chronic course. Untreated autoimmune hepatitis may develop liver cirrhosis and its complications. The majority of patients responds well to predniso(lo)ne with or without azathioprine, the so called standard of care (SOC)[1, 2]. Normalization of both, aminotransferases and immunoglobulin G, is the goal of treatment and defines complete remission. Patients under complete remission usually do not progress and patients enjoy a normal life expectancy[1-3].

The patients are started on high dose induction therapy and once remission is achieved patients are kept at an individualized low dose maintenance therapy. A proportion of patients, while under complete remission for at least 2 years, can terminate immunosuppressive therapy without experiencing a relapse. However, the majority of patients requires life-long maintenance immunosuppressive therapy[4]. Second-line therapies are needed, if patients fail to achieve complete remission or if patients are intolerant to immunosuppressive medication. Bone marrow suppression is the major safety signal for azathioprine toxicity, while steroid specific side effects (SSSE) like moon face, acne, buffalo hump, hirsutism, striae, diabetes, and glaucoma often occur in patients treated with predniso(lo)ne[2].

Budesonide is a synthetic glucocorticoid with an over 90% hepatic first pass effect and therefore low corticosteroid bioavailabilty and low SSSEs. It was first tested in AIH patients more than 20 years ago and showed improvement of liver inflammatory activity without exhibiting SSSEs[5]. Subsequently 10 studies and several case reports were published on the use of budesonide in AIH with varying success (Table 1). There is just one prospective multicenter randomized trial in the literature comparing budesonide vs. prednisone as first-line therapy[6]. Based on the results of this study budesonide was approved for autoimmune hepatitis in combination with azathioprine in several European and non-European countries.

Since budesonide acts via the same corticosteroid receptor as predniso(lo)ne it is logical that budesonide should not be used in patients not responding to predniso(lo)ne. Budesonide when combined with azathioprine seems to be equally effective as first-line regimen and at the same time causing less steroid specific side effects[6-8].

Until recently our knowledge on budesonide as second-line therapy was rather limited[9-11]. It was based on 36 patients treated with budesonide alone. Remission rates varied between 30% and up to 100% (according to the old AASLD definition of achieving aminotransferase levels below 2 times the upper limit of normal). Patients switching to budesonide in these early studies were rather heterogeneous. First line treatment had failed due either to incomplete remission, prednisolone intolerance or prednisolone dependency. Furthermore cirrhotic patients were not excluded. These patients do not benefit as much from the high first past effect and may develop hepatic vein thrombosis and severe systemic infections as shown in other studies for different indications[12, 13]. Therefore budesonide is not approved for AIH patients with cirrhosis.

The study by Peiseler, Liebscher et al.[14] published in this issue of *Clinical Gastroenterology and Hepatology* tries to overcome these limitations by (I) publishing the largest cohort of AIH patients (n = 60) and the longest budesonide treatment surveillance so far as second-line therapy (31 months in average), (II) reporting on the combination of budesonide with azathioprine and other immunosuppressants used as second-line therapy, (III) carefully distinguishing the patients switched to budesonide either because of prednisolone dependency or due to corticosteroid-induced side effects and (IV) excluding patients with overlap syndromes and cirrhosis. Patients analysed in the present single center retrospective analysis not only were difficult to manage in terms of SSSEs or prednisolone dependency but at the same time included patients with incomplete biochemical response. However, long term remission was achieved with budesonide in approximately 40-45% of these difficult-to-treat AIH patients and thereby doubled the initial remission rate. Budesonide could also be stopped in eight of these patients (13%). Several patients were withdrawn from budesonide

subsequently and switched back to other therapies. Reasons were insufficient disease control (flares and development of cirrhosis) in 14/60 (23%) patients, side effects in 8/60 (13%).

Data on potential long term benefits of the topical steroid budesonide on bone density had not been reported before and were eagerly awaited for. The study by Peiseler et al.[14] for the first time provides data on bone density. In most patients bone density was stable or improved in longitudinal assessment. These data encourage further future long term studies on bone density under budesonide therapy.

The study does not answer the question, which regimen (budesonide alone or in combination with other immunosuppressive agents) is the most favorable budesonide based second-line therapy. Although some patients had surveillance liver biopsies in the course of the study, results are not systematically reported. Thus data on histological remission in budesonide treated AIH patients, either after first- or second-line therapy, still remain to be shown.

The lower remission rates in the current second-line study are most likely caused by enrichment in patients in whom remission is difficult to achieve with steroids. Mechanisms of insufficient disease control could be the high first pass effect of budesonide itself. Thereby, low systemic budesonide levels, which are on one hand responsible for the low SSSEs, may be insufficient to suppress the formation or persistence of long-lived memory cells in primary and secondary lymphoid organs (spleen, lymph nodes and bone marrow). The fact that the normalization of immunoglobulins was achieved later in budesonide compared to prednisone treated patients points in the same direction[6]. Since AIH is associated with extrahepatic manifestations and extrahepatic autoimmune diseases, insufficient extrahepatic disease control due to low systemic steroid doses can also lead to a discontinuation of budesonide, as reported in 2/60 patients in the current study[14].

Budesonide can induce remission in some but by far not all patients pretreated with predniso(lo)ne. Stronger suppression of the autoimmune attack towards the liver remains a

challenge in a substantial proportion of AIH patients failing to standard of care. Additional drugs with different modes of action need to be explored for such difficult to treat patients. Foremost, calcineurin inhibitors are widely used in autoimmune diseases including AIH and are well established in patients after liver transplantation, a different setting with an often strong alloimmune response against the liver. Other approaches, mostly reported for small numbers of patients from single centers include therapies with monoclonal antibodies against the B cell surface marker CD 20 like rituximab or TNF alpha like infliximab[15]. In the near future a further biological, anti-BAFF receptor antibody VAY736, will be tested in a multicenter trial (NCT03217422) in AIH patients with incomplete response or intolerance to standard therapy.

In addition, steroid and azathioprine based therapies are leading to a preferential depletion of regulatory T cells over effector T cells, thereby potentially disturbing the long-term intrahepatic immune tolerance[16, 17]. This local reduction of regulatory T cells seems to be associated with a worse treatment response potentially mediated by the lack of their survival factor IL-2[16-18]. This might be one reason for relapses frequently observed after discontinuation of immunosuppressive therapy. With these recent pathophysiological insights into the intrahepatic immune milieu under therapy and in patients with incomplete treatment response pharmacologically different and innovative approaches should be considered. mTOR inhibitors like rapamycin promote immune regulation, current data on their use in AIH are too limited to allow any conclusion. Preliminary results on the use of low dose IL-2 to support regulatory T cells are promising in other (auto)immune mediated diseases[19] which may also be explored in AIH.

In summary, there is a clear clinical need for more innovative second-line therapies for AIH. Hopefully ongoing initiatives will lead to a consensus approach for the development of effective second-line therapies for this difficult to treat group of patients. The current study by Peiseler, Liebscher and colleagues[14] is an important step forward in our understanding of the potential long term benefits of budesonide even as second-line therapy. However,

budesonide primarily remains an alternative to predniso(lo)ne as a component of first-line therapy for AIH in order to achieve better long term tolerability.

References

1. European Association for the Study of the L. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63(4):971-1004.
2. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51(6):2193-213.
3. Muratori L, Muratori P, Lanzoni G, et al. Application of the 2010 American Association for the study of liver diseases criteria of remission to a cohort of Italian patients with autoimmune hepatitis. Hepatology. 2010;52(2):1857-8.
4. van Gerven NM, Verwer BJ, Witte BI, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol. 2013;58(1):141-7.
5. Danielsson A, Prytz H. Oral budesonide for treatment of autoimmune chronic active hepatitis. Alimentary pharmacology & therapeutics. 1994;8(6):585-90.
6. Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010;139(4):1198-206.
7. Woynarowski M, Nemeth A, Baruch Y, et al. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. J Pediatr. 2013;163(5):1347-53 e1.
8. Delgado JS, Vodonos A, Malnick S, et al. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. Journal of digestive diseases. 2013;14(11):611-8.
9. Csepregi A, Rocken C, Treiber G, et al. Budesonide induces complete remission in autoimmune hepatitis. World journal of gastroenterology. 2006;12(9):1362-6.

10. Czaja AJ, Lindor KD. Failure of budesonide in a pilot study of treatment-dependent autoimmune hepatitis. Gastroenterology. 2000;119(5):1312-6.

11. Zandieh I, Krygier D, Wong V, et al. The use of budesonide in the treatment of autoimmune hepatitis in Canada. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2008;22(4):388-92.

12. Mederacke I, Helfritz F, Puls F, et al. Budd-Chiari syndrome after treatment with budesonide in a cirrhotic patient with autoimmune hepatitis. Annals of hepatology. 2012;11(1):143-4.

13. Hempfling W, Grunhage F, Dilger K, et al. Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. Hepatology. 2003;38(1):196-202.

14. Peiseler M, Liebscher T, Sebode M, et al. Efficacy and Limitations of Budesonide as a Second-Line Treatment for Patients With Autoimmune Hepatitis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2017.

15. Czaja AJ. Current and prospective pharmacotherapy for autoimmune hepatitis. Expert opinion on pharmacotherapy. 2014;15(12):1715-36.

16. Diestelhorst J, Junge N, Schlue J, et al. Pediatric autoimmune hepatitis shows a disproportionate decline of regulatory T cells in the liver and of IL-2 in the blood of patients undergoing therapy. PloS one. 2017;12(7):e0181107.

17. Taubert R, Hardtke-Wolenski M, Noyan F, et al. Intrahepatic regulatory T cells in autoimmune hepatitis are associated with treatment response and depleted with current therapies. J Hepatol. 2014;61(5):1106-14.

18. Chen YY, Jeffery HC, Hunter S, et al. Human intrahepatic tregs are functional, require IL-2 from effector cells for survival and are susceptible to fas ligand mediated apoptosis. Hepatology. 2016.

19. Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. Nature reviews Immunology. 2015;15(5):283-94.

20. Efe C, Ozaslan E, Kav T, et al. Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome. Autoimmunity reviews. 2012;11(5):330-4.

21. Wiegand J, Schuler A, Kanzler S, et al. Budesonide in previously untreated autoimmune hepatitis. Liver international : official journal of the International Association for the Study of the Liver. 2005;25(5):927-34.

Table 1: Published studies on budesonide use in autoimmune hepatitis (AIH)

	Study		Patients	Drugs	Treatment duration (mean, (range))	Treatment response	p-value	steroid-specific side effect	p-value
First-line therapy	Delgado et al. 2013[8]	multicenter retrospective	11	budesonide/ azathioprine	"at least 24 months"	64% CBR	not significant	not reported specifically	
			71	prednisone/ azathioprine		55% CBR			
			10	budesonide		9% CBR			
			6	prednisone		17% CBR			
	Efe et al. 2012[20]	multicenter retrospective	14#	budesonide/ azathioprine	10 months (2-24 months)	71 % BR		not reported specifically	
	Manns et al. 2010[6]	multicenter RCT	102	budesonide/ azathioprine	6 months	60% BR	<0.001	28%	<0.001
			105	prednisone/ azathioprine		39% BR		53%	
	- Woynarowski et al. 2013[7]	*multicenter RCT (pediatric sub-cohort of Manns et al. 2010[6])*	*19*	*budesonide/ azathioprine*	*6 months*	*32% BR*	*not significant*	*47%*	*not significant*
			27	*prednisone/ azathioprine*		*33% BR*		*63%*	
	Csepregi et al. 2006[9]	multicenter open label	7# (3x with advanced fibrosis)	budesonide	8 months (1-12 months)	57% BR		33% (overall)	
	Wiegand et al. 2005[21]	multicenter open label	12	budesonide	3 months	58% BR§		not reported specifically	
Second-line therapy	Peiseler, Liebscher et al. 2017[14]	single center retrospective	40	budesonide/ azathioprine	31 months (6-99 months)	45 % BR		not reported specifically	
			10	budesonide					
			10	budesonide + 2nd immunosuppressant					
	Zandieh et al. 2008[11]	multicenter retrospective	9	budesonide (2x with azathioprine)	25 month (6-96 months)	78% BR		not reported specifically	
	Csepregi et al. 2006[9]	multicenter open label	4#	budesonide	21 months (12-29 months)	100% BR		33% (overall)	
	Czaja and Lindor 2000[10]	single center open label	10 (including 2 cirrhotics)	budesonide	5 months (2-12 months)	30% BR§		30%	
	Danielsson and Prytz 1994[5]	single center open label	13 (including 7 cirrhotics)	budesonide	"up to 9 months"	improvement of aminotransferases and			

						immunoglobulins			

[#] overlap syndromes excluded; [§] according to old definition < 2x upper limit of normal; BR: biochemical remission; CBR: clinical and biochemical remission; RCT= randomized controlled trial