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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
ESPS Manuscript NO: 7144
Title: Management of Autoimmune Hepatitis: focus on pharmacologic treatments beyond corticosteroids.
Reviewer code: 02447151
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-06 09:31
Date reviewed: 2013-11-12 19:32

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS
This is a review article to identify the efficient rescue treatments options for the difficult-to-treat AIH patients. It is very important for treating these patients. However, there are several comments: Major comments 1. AIH patients in Asian countries are different from Caucasian patients with regard to treatment efficacy and long-term outcomes. AIH papers from Asian countries should be referred and discussed. In ursodeoxycholic acid section, Miyake's paper (Hepatol Int 2009; 3: 556-629) should be referred. 2. In the references, there are many mistakes. For example, is author's name PJ., J. in the reference #21? EL., K. in #24? Reference form should be united. 3. In rituximab section, phase I rituximab trial study is reference #49 not #48. Furthermore, #49 should be changed to the same author's paper ' Rituximab for the treatment of patients with autoimmune hepatitis …' in Can J Gastroenterol 2013; 27: 273-280. Minor comments 1.Line 12 in rituximab section; there is a misspelling. secondary o azathioprine.

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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
ESPS Manuscript NO: 7144
Title: Management of Autoimmune Hepatitis: focus on pharmacologic treatments beyond corticosteroids.
Reviewer code: 02462024
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-06 09:31
Date reviewed: 2013-11-18 01:19

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[Y] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
There are a number of major flaws/omissions here as follows: 1. there is no mention of budesonide- this pred alternative is fairly well studied in non-cirrhotic AIH and reduces many of the traditional pred-related side effects 2. there is no mention of utility of AZA metabolite level measurements and more importantly the role of allopurinol in improving side-effects associated with AZA and allowing continuation. This I believe is potentially the most significant and yet simple recent advance in AIH as opposed to other less well established and effective therapies 3. Some of the data regarding relapse rates as well as remission rates with standard therapies are somewhat outdated with new evidence emerging to suggest that actual remission rates are lwoer and relapse almost universal if monitored for long enough after drug withdrawal Overall, there needs to be significant revision and updating of data and discussions prior to this being acceptable including some improvement in the use of English

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ESPS Peer-review Report
Name of Journal: World Journal of Hepatology
ESPS Manuscript NO: 7144
Title: Management of Autoimmune Hepatitis: focus on pharmacologic treatments beyond corticosteroids.
Reviewer code: 01836203
Science editor: Zhai, Huan-Huan
Date sent for review: 2013-11-06 09:31
Date reviewed: 2013-11-19 15:14

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[ ] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[Y] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[ ] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[Y] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
The manuscript " Management of Autoimmune Hepatitis: Focus on pharmacologic treatments beyond corticosteroids" deals with second- and third-line treatment options for the treatment of autoimmune hepatitis. This is an important topic with no evidence from controlled studies. Therefore expert opinion is paramount in this field and the published series should be interpreted with caution. Although the topic is of interest, the manuscript needs revision before it is suitable for publication. Throughout the manuscript, as this is a review article itself, it would be better to cite original articles rather than to refer to review articles. Cost should be mentioned as these newer agents are much more expensive than standard treatment. In this regard the cheaper alternatives 6MP and also the measurement of azathioprine metabolites, as recently published should be discussed. Also, the difficult to treat groups could be better defined. There is a great difference between patients intolerant to aza or having a relapse as compared to patients not responding to initial treatment or fulminant presentation. This holds especially true for the treatment data on MMF. Table 1 should be modified: include the substance studied, the number of patients included (adults/peds), the indication used in the study, omit the side effects, but mention success rates (complete, incomplete remission) and the duration of treatment. For matters of completeness, I would suggest to also discuss budesonide1 as an "alternative" steroid for the treatment of AIH. It would also be nice to hear some words about quality of life and adherence in these patients, as especially adherence may be extremely important for induction of remission2. Further on, the part on standard treatment should be revised (pls. see below) as several different treatment regimes may be used. Page 5: As many patients present with arthralgias as one of the main symptoms, it should be mentioned. Page

6: "The presence of cirrhosis is associated with a mortality rate of 58% within 5 years". It is not clear whether the whole paragraph relates to patients without treatment or not. If under treatment this statement is false. In addition, the prognosis of disease is influenced by age (young patients having an increased risk), presence of cirrhosis, treatment response (as opposed to activity) and relapses. Page 8: Relapse is almost universal in patients with AIH and usually occurs when tapering out treatment. In the vast majority of the patients, a relapse can be treated with the same regime as the initial AIH was treated and usually has excellent success rates. A flare – i. e. increasing disease activity under ongoing treatment – classifies most of the patients as "difficult to treat". I would therefore advise to clarify terminology. As a recent reference including a large number of patients the recent paper by the Dutch Study Group published in J Hep should be cited. Page 8: histological remission should be differentiated from biochemical remission, for which the current definition is complete normalization of aminotransferase levels including IgG. Treatment should definitely be considered in any patient with proven AIH and histological activity and a more than marginal elevation of aminotransferase levels, not only in patients with levels greater 5xULN, this should be commented on. Page 9: PSC and PBC should not be abbreviated. The authors state that prednisolone used for monotherapy should be maintained for 6 months at a dose of 20mg/day. It should be clearly stated, that monotherapy is not the treatment of first choice, as it will inevitably lead to Cushing syndromes. It is also of debate, whether steroid treatment should really start in a lower dose when combining with azathioprine, as it has been clearly shown that higher doses are associated with a higher percentage of response.3 Results reported from large European centers seem to be better than those from US American