

Evidence-Based Medicine Conference

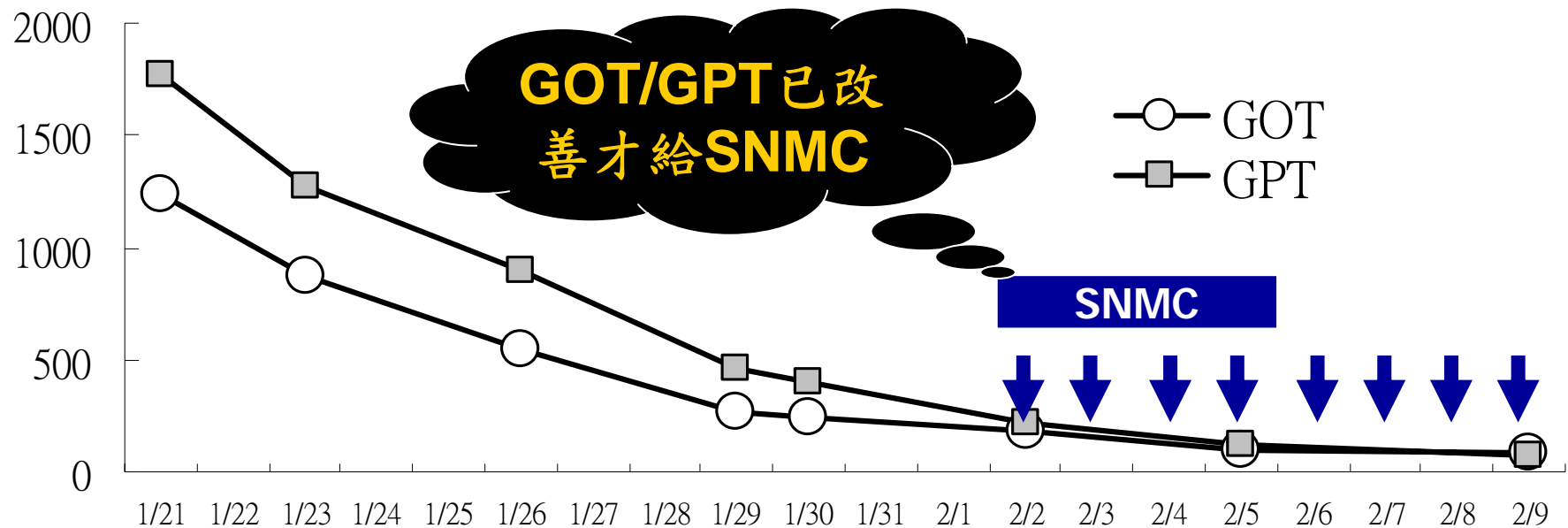
實證醫學在臨床藥學上的應用

藥劑部UD藥局 蘇富敏藥師

Clinical Scenario

個案病例摘要

- Name : 莊00
- Age / Sex : 43 / M
- BW / BH : 66 kg / 173 cm
- Chart No. : 19278***
- HBV(+)
- HCV(-)



Clinical Scenario

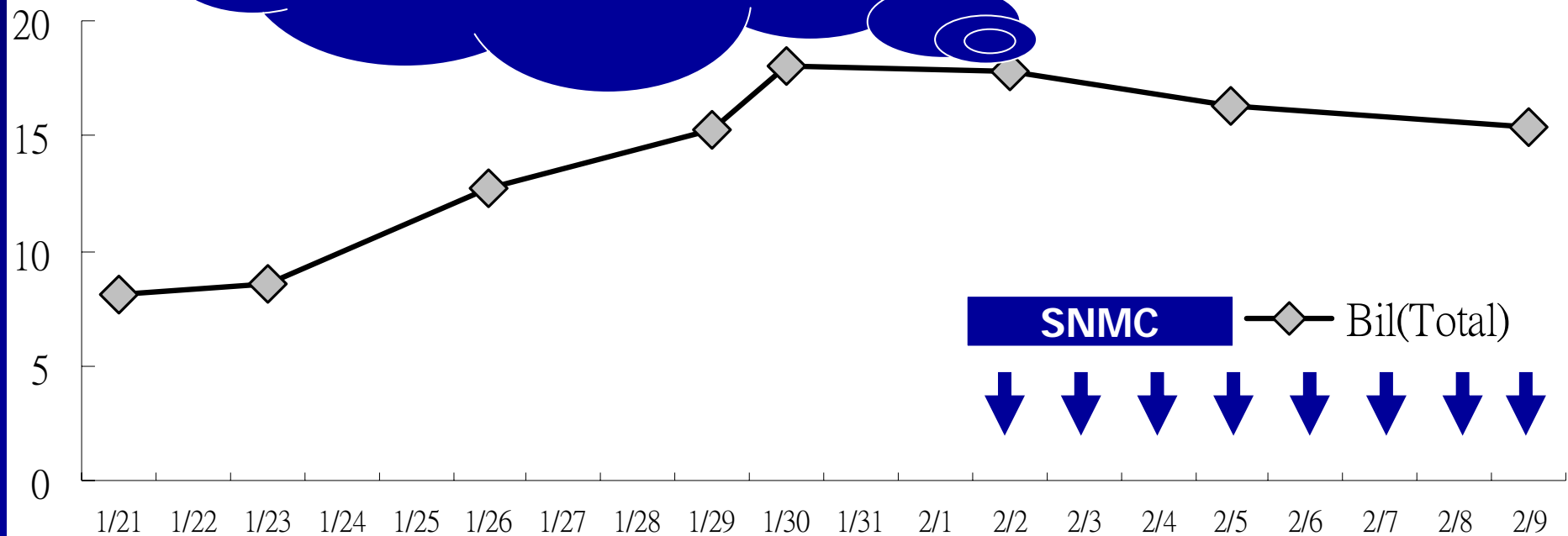
個案病例摘要

黃疸沒退才給
SNMC，但治療後黃
疸似乎也沒明顯改善

Chart No. : 19278***

HBV(+)

HCV(-)



病人問的問題

- 我自費接受Stronger Neo-Minophagen C治療肝炎或黃疸是否有效？

Asking Answerable Clinical Questions

Background Questions

- 如何診斷肝炎／黃疸？
- 肝炎／黃疸的病理生理機轉為何？
- 肝炎／黃疸的分類有那幾種？
- 肝炎／黃疸的治療時機為何？
- 肝炎／黃疸的治療方法有哪些？
- 肝炎／黃疸的併發症及預後有哪些？

Foreground Question

**SNMC (Stronger
Neo-Minophagen C)**

治療肝炎或黃疸是否有效？

Asking Answerable Clinical Question (PICO)

■ *Patient and /or Problem*

- Patient with Hepatitis/Jaundice

■ *Intervention (treatment)*

- Stronger Neo-Minophagen C (SNMC)

■ *Comparison Intervention*

- Without SNMC

■ *Clinical Outcome*

- Biochemical response (Serum Bilirubin 、 GOT 、 GPT)
- Virologic response
- Serologic Response
- Histologic response

Acquire ----- 搜尋最有用資料

- Database:
 - Cochrane Library
 - EBMR
 - ACP Journal Club
 - Database of Abstracts of Reviews of Effectiveness
 - Medline
 - PubMed
- Key Words:
 - Stronger Neo-Minophagen C AND Jaundice
 - Stronger Neo-Minophagen C AND (Chronic Hepatitis B OR Alcoholic Hepatitis)

資料評估準則

Levels of Evidence

Oxford Centre for Evidence-Based Medicine

Level	Therapy/Prevention, Aetiology/Harm
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow CI)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT)
2c	"Outcomes" Research; Ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Stronger Neo-Minophagen C AND (chronic hepatitis B OR alcoholic hepatitis)

Stronger Neo-Minophagen C AND jaundice

Searching Results

Jaundice

■ Database:

- Cochrane Library (0)
- EBMR (0)
- ACP Journal Club (0)
- Medline/Pub-Med (Case Report:1)

Searching Result

SNMC對藥物引起黃疸可能有效

Pub-Med

目前只有一篇 Case Report。

- Ishii M, Miyazaki Y, Yamamoto T, Miura M, Ueno Y, Takahashi T, Toyota T. A case of drug-induced ductopenia resulting in fatal biliary cirrhosis. *Liver*. 1993 Aug;13(4):227-31. (LOE: 4)

Searching Results

Chronic Hepatitis B OR Alcoholic Hepatitis

■ Database:

- Cochrane Library (0)
- EBMR (0)
- ACP Journal Club (0)
- Medline/Pub-Med (3)
 - RCT (1)
 - Case Report/ Case Series (2)
 - Review (0)

Searching Results

PubMed

- Zhang L, Wang B. Randomized controlled trial of 100 and 40 ml of Stronger Neo-minophagen C in Chinese patients with chronic hepatitis B. *Hepatol Res.* 2002 Nov;24(3):220-227. (LOE: 2)
- Takaki A, Nakatsuka A, Satou C, Iwata Y, Ikeda H, Fukushima M. A case of focal segmental glomerulosclerosis (FSGS) complicated with chronic hepatitis B and treated with steroid and LDL apheresis. *Nippon Jinzo Gakkai Shi.* 2002 Dec;44(8):806-12. (LOE: 4)
- Sumiyama K, Kobayashi M, Miyashiro E, Koike M. Combination therapy with transfer factor and high dose stronger neo-minophagen C in chronic hepatitis B in children (HBe Ag positive). *Acta Paediatr Jpn.* 1991 Jun;33(3):327-34. (LOE: 4)

目前已發表的SNMC治療慢性B型肝炎文獻中，只有一篇RCT。因此進行本篇論文評讀。

Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. Hepatol Res. 2002 Nov;24(3):220-227

Appraisal

by CASP (Critical Appraisal Skills Programme)

1. Did the study ask a clearly-focused question?
2. Was this a randomised controlled trial (RCT) and was it appropriately so?
3. Were participants appropriately allocated to intervention and control groups?
4. Were participants, staff and study personnel 'blind' to participants' study group?
5. Were all of the participants who entered the trial accounted for at its conclusion?

Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. Hepatol Res. 2002 Nov;24(3):220-227

Appraisal

by CASP (Critical Appraisal Skills Programme)

6. Were the participants in all groups followed up and data collected in the same way?
7. Did the study have enough participants to minimise the play of chance?
8. How are the results presented and what is the main result?
9. How precise are these results?
10. Were all important outcomes considered so the results can be applied?



Appraisal

by CASP (Critical Appraisal Skills Programme)

1. Did the study ask a clearly-focused question?

Yes Can't tell No

- Consider if the question is 'focused' in terms of:
 - the population studied
 - the intervention given
 - the outcomes considered

Comment:

- There are clear Inclusion / Exclusion Criteria to focus the studied population, intervention, and the outcomes



Inclusion Criteria

- Fulfill diagnostic criteria in the national programme for prevention of viral hepatitis in 1995.
- 16-65 years old
- Serum ALT > 2 times the upper limit of normal (ULN)

- 未提及HBV-DNA
- 未證明此次肝炎發作是因B型肝炎造成，而無其他病因造成。



Exclusion Criteria

- Serum Bilirubin $> 85 \mu\text{mol/l}$ (5 mg/dl)
- Receiving Interferon or Antiviral drugs during 1 month before
- Co-infection with HCV

未提及

- 1) Co-infection with HDV or HIV
- 2) Other forms of liver disease
- 3) Use of thymosin- α 1
- 4) α -fetoprotein (AFP) > 100
ng/mL



Appraisal

by CASP (Critical Appraisal Skills Programme)

2. Was this a randomised controlled trial (RCT) and was it appropriately so?

Yes Can't tell No

■ Consider:

- *why this study was carried out as an RCT*
- *if this was the right research approach for the question being asked*

Comment:

- This was an experimental study with randomization, double-blind, active controlled trial.
- This was the right research approach for the question being asked



Appraisal

by CASP (Critical Appraisal Skills Programme)

3. Were participants appropriately allocated to intervention and control groups?

Yes Can't tell No

■ Consider:

- *how participants were allocated to intervention and control groups. Was the process truly random?*
- *whether the method of allocation was described. Was a method used to balance the randomization, e.g. stratification?*
- *how the randomization schedule was generated and how a participant was allocated to a study group*
- *if the groups were well balanced. Are any differences between the groups at entry to the trial reported?*
- *if there were differences reported that might have explained any outcome(s) (confounding)*

Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. Hepatol Res. 2002 Nov;24(3):220-227

Appraisal

by CASP (Critical Appraisal Skills Programme)

3. Were participants appropriately allocated to intervention and control groups?

Comment:

- Patients were randomized by the randomization table.
- The 2 treatment groups were well-balanced for demographics and disease characteristics at baseline

Well-Balanced Demographics and Disease Characteristics at Baseline

Features	Group A (100 ml) (<i>N</i> = 99)	Group B (40 ml) (<i>N</i> = 95)
Male	84 (85%)	79 (83%)
Age (years)	33.9 ± 10.7	34.7 ± 10.1
ALT (IU/l)	295 ± 252	290 ± 243
AST (IU/l)	194 ± 187	207 ± 195
γ-GTP (IU)	101 ± 80	83 ± 57
Bilirubin (μmol/l)	28.9 ± 22.5	29.7 ± 32.1
HBeAg	58 (59%)	57 (60%)



Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. Hepatol Res. 2002 Nov;24(3):220-227

Appraisal

by CASP (Critical Appraisal Skills Programme)

4. Were participants, staff and study personnel 'blind' to participants' study group?

Yes Can't tell No

■ *Consider:*

- *the fact that blinding is not always possible*
- *if every effort was made to achieve blinding*
- *if you think it matters in this study*
- *the fact that we are looking for 'observer bias'*

Comment: Not mentioned.



Appraisal

by CASP (Critical Appraisal Skills Programme)

5. Were all of the participants who entered the trial accounted for at its conclusion?

Yes Can't tell No

■ *Consider:*

- *if any intervention-group participants got a control-group option or vice versa*
- *if all participants were followed up in each study group (was there **loss-to-follow-up**?)*
- *if all the participants' outcomes were analysed by the groups to which they were originally allocated (**intention-to-treat analysis**)*
- *what additional information would you liked to have seen to make you feel better about this*

Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. Hepatol Res. 2002 Nov;24(3):220-227

Appraisal

by CASP (Critical Appraisal Skills Programme)

5. Were all of the participants who entered the trial accounted for at its conclusion?

Comment:

- The treatment was withdrawn in only two patients each in Groups A and B due to thoracic distress and elevated blood pressure.
- Statistical analysis did not mention any about intention-to-treat method and the method to deal with *loss-to-follow-up*.



Appraisal

by CASP (Critical Appraisal Skills Programme)

6. Were the participants in all groups followed up and data collected in the same way?

Yes Can't tell No

■ *Consider:*

- *if, for example, they were reviewed at the same time intervals and if they received the same amount of attention from researchers and health workers. Any differences may introduce performance bias.*



Appraisal

by CASP (Critical Appraisal Skills Programme)

7. Did the study have enough participants to minimise the play of chance?

Yes Can't tell No

■ Consider:

– *if there is a power calculation. This will estimate how many participants are needed to be reasonably sure of finding something important (if it really exists and for a given level of uncertainty about the final result).*

Comment:

- **No power calculation.**



Appraisal

by CASP (Critical Appraisal Skills Programme)

8. How are the results presented and what is the main result?

Yes Can't tell No

■ *Consider:*

- *if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or median differences, or as survival curves and hazards*
- *how large this size of result is and how meaningful it is*
- *how you would sum up the bottom-line result of the trial in one sentence*

Appraisal by CASP (Critical Appraisal Skills Programme)

Duration of SNMC

Normalization in

	ALT levels		AST levels	
	Group A (N = 99)	Group B (N = 95)	Group A (N = 99)	Group B (N = 95)
4 weeks	28 (28%)			33 (35%)
8 weeks ^a	56 (57%)			52 (55%)
	ALT			
	Group A			
Pretreatment	295 ± 252			221
4 weeks	88 ± 78			13 ± 12.8
8 weeks ^a	53 ± 49			16.1 ± 11.6

Group A (100ml) v.s. group B (40ml). No control group (0ml). Lack of dose-dependent respons. Natural course could not be ruled out.

Appraisal by CA

Lack of histologic response,
virologic response. Only
biochemical and serologic
response

Comments

- Decrease in ALT levels to ≤ 1.5 times ULN in approximately 50% at week 4 and $> 70\%$ at week 8 for patients in both Groups A and B ($P > 0.05$).
- No patients lost HBsAg from serum.
HBeAg turned negative in Group A (16%) and Group B (25%).
Seroconversion to anti-HBe occurred in Group A (5%) and Group B (11%). (all Non-Significant)



Appraisal

by CASP (Critical Appraisal Skills Programme)

9. How precise are these results?

Yes Can't tell No

■ Consider:

- *if the result is precise enough to make a decision*
- *if a confidence interval were reported. Would your decision about whether or not to use this intervention be the same at the upper confidence limit as at the lower confidence limit?*
- *if a p-value is reported where confidence intervals are unavailable*

Comment:

- Significant p-value is reported ($P < 0.05$).
- Confidence interval was not reported.



Appraisal

by CASP (Critical Appraisal Skills Programme)

10. Were all important outcomes considered so the results can be applied? Yes Can't tell No

- Consider whether:
 - the people included in the trial could be different from your population in ways that would produce different results
 - your local setting differs much from that of the trial
 - you can provide the same treatment in your setting
- Consider outcomes from the point of view of the:
 - individual
 - policy maker and professionals
 - family/carers
 - wider community
- Consider whether:
 - any benefit reported outweighs any harm and/or cost. If this information is not reported can it be filled in from elsewhere?
 - policy or practice should change as a result of the evidence contained in this trial

Appraisal by CASP (Critical Appraisal Skills Programme)

Comment:

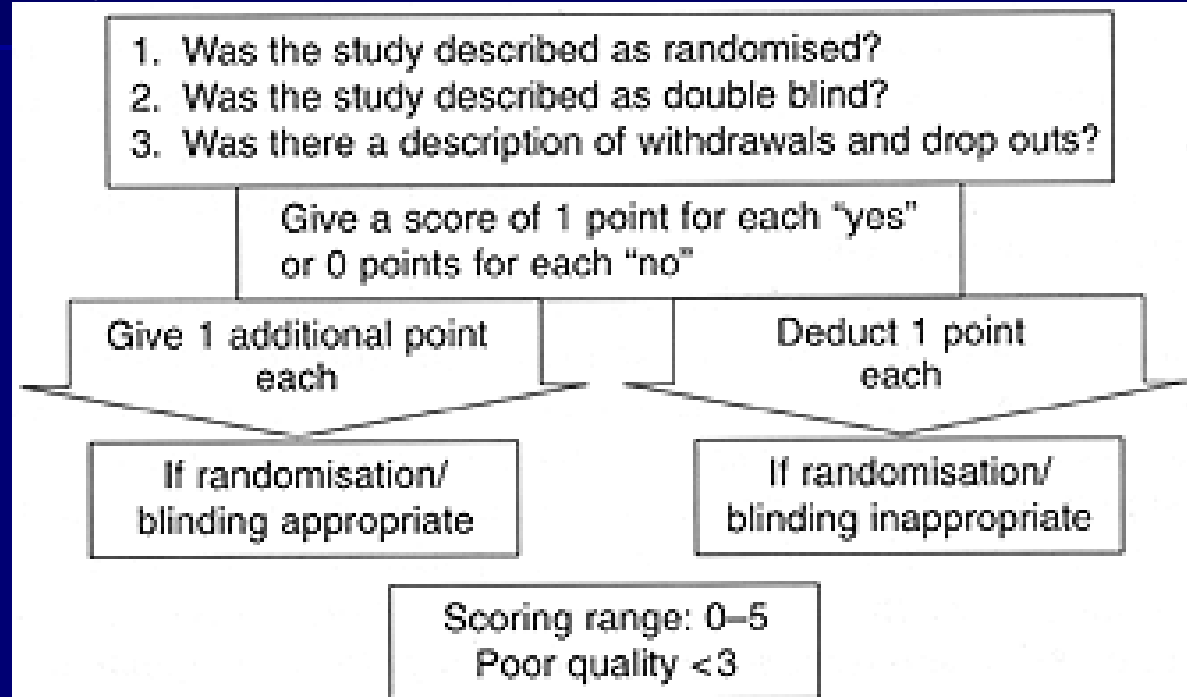
- Different biochemical characteristics of our patient. Patients with serum bilirubin $> 85 \mu\text{mol/l}$ (5 mg/dl) were excluded but our patient had severe jaundice ($> 5 \text{ mg/dl}$).
- NNT cannot be calculated without control group.
- No difference of biochemical and serologic response between Group A and B.
- No histologic and virologic response to validate the effect.



Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. *Hepatol Res.* 2002 Nov;24(3):220-227

Appraisal

RCT Scoring System (1)----Jadad Scale



- Randomization (2)
- Double blinding (0)
- Completeness of follow up (1)

Total Score: 3

Figure 4.1 Validated quality scale. (From Jadad et al.¹)

Appraisal

RCT Scoring System (2)

本論文得分



- Selection and homogeneity (6 points) ----- 1
 - Inclusion and exclusion criteria clearly described: 1
 - Investigation confined to a homogeneous study population: 5
- Design (11 points) ----- 11
 - Randomised design (described): 4
 - Randomisation procedure adequate: 7
 - Randomisation procedure inappropriate: -3
- Comparability of groups (9 points : 1 each) ----- 4
 - Groups comparable for duration of disease, age, sex, treatment, co-morbidity, coping behaviour, social economic status, social network and baseline outcome measure ◦

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Appraisal

RCT *Scoring System (2)*

本論文得分



- Drop out handling (6 points) ----- 6
 - Drop-outs <10%, < 30%, <50%: 3, 2, and 1 point
 - Number drop-out presented every group: 1
 - Reasons drop-out mentioned: 2
- Number of patients in the smallest group included (15 points) ----- 15
 - >25 patients: 6
 - >50 patients: 9
 - >75 patients: 15

Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. *Hepatol Res.* 2002 Nov;24(3):220-227

Appraisal

RCT *Scoring System* (2)

本論文得分



- Description of intervention and control (15)-----7
 - Participants in intervention / control described: 3 each
 - Intervention / control described adequately: 4 each
 - Described partially: half
 - Site of intervention mentioned: 1
- Simultaneous interventions (6) -----6
 - No simultaneous interventions: 6
 - Comparable simultaneous interventions: 3

Appraisal

RCT *Scoring System* (2)

本論文得分



- Blind assessor collecting outcome measures (5) -----0
- Use appropriate outcome measures (8) -----4
 - Term “outcome” clarified: 2
 - Outcome measured in a multidimensional way: 2
 - Explain why test was used: 2
 - Patients judge their own: 2
- Follow-up (6) -----3
 - Outcome collected in intervention / control at equal intervals: 3
 - Outcome collected > 1 month after intervention start: 3

Appraisal

RCT Scoring System (2)

本論文得分



■ Statistical analysis (10) -----4

- Examine possibility of selection bias owing to drop-out: 1
- Drop-out was not selective: 3
- Corrected for possible confounding factors / no confounding factors: 0

■ Data presentation (10) -----0

- Authors present a dependent variable (s): 0

**Poor quality RCT.
Levels of Evidence: 2b**

Total Score: 61

Zhang L, Wang B. Randomized clinical trial with two doses (100 and 40 ml) of Stronger Neo-Minophagen C in Chinese patients with chronic hepatitis B. Hepatol Res. 2002 Nov;24(3):220-227

Possible Bias

- Double-blinding has not been mentioned that imply a possible performance bias.
- No control group to rule out the possibility of natural course. Lack of dose-dependent response of SNMC can possibly imply a natural course.
- Lack of HBV-DNA data to select patients that can include non-HBV related hepatitis.
- Lack of histologic response and virologic response. Only biochemical response and serologic response cannot make a tough conclusion of the effect of SNMC.
- Lack of ITT analysis is not important here.

Application

(Usefulness in our clinical practice)

- 無足夠證據顯示SNMC對黃疸病人或B型肝炎病人有效。
- 應等更多更強有力的證據支持其效果後，再應用於病人身上。

謝謝您

- Thank You
- Merci
- Danke
- Gracias
- Grazie
- あなたに感謝しなさい
- 너를 감사하십시오
- Спасибо
- الشكر؛ شكر
- 谢谢