EBM Journal Club

Rheumatoid Arthritis : Is *Tripterygium wilfordii* Hook F a remedy?

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時間地點：2015/10/21 PM12:30 台北中醫門診B1會議室

OUTLINE

- Background
- Scenario
- Ask(PICO)
- Aquire
- Appraisal
- Apply
- Audit

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BACKGROUND

- 類風濕性關節炎(rheumatoid arthritis, RA)是一 種慢性、全身進展性的自體免疫疾病。
- 不同種族 有不同的盛行率，美國盛行率約0.6%，台灣盛行率約0.8%
- 女性發生率約為男性的三倍，好發於35-50歲成年人。
- 常見有骨頭關節發炎、疼痛和受傷，可 能會侵犯內臟、血管、神經...等而導致全身疲倦、 體重減輕、食慾不振等症狀

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Clinical manifestation of RA

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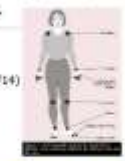
類風濕關節炎診斷準則

美國風濕病學會



(1) 晨間僵硬
(2) 三個以上關節區之關節炎(>=3/14)
(3) 手部關節炎 (PIP, MCP, wrist)
(4) 對稱性關節炎
(5) 類風濕結節
(6) 血清類風濕因子~ RF陰性反應(15%)並不能排除類風濕性關節炎的可能性
(7) X光片變化

*符合上述7項準則中至少4項者，可診斷為類風濕關節炎（第1至第4項需持續六週以上）

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1987 American College of Rheumatology (formerly American Rheumatism Association) revised classification criteria for rheumatoid arthritis

Criterion	Description
Morning stiffness	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.
Arthritis of three or more joint areas	At least three joint areas (out of 14 possible areas): right or left PIP, MCP, wrist, elbow, knee, ankle, MTP joints) simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) as observed by a physician.
Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs, without absolute symmetry is acceptable).
Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions as observed by a physician.
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5 percent of normal control subjects.
Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand or wrist radiographs, which must include erosion or unequivocal bony decalcification localized in, or most marked adjacent to, the involved joints (osteoarthritis changes alone do not qualify).

Note: For classification purposes, a patient has RA if at least four of these criteria are satisfied (the first four must have been present for at least six weeks).

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2010年ACR/EULAR(American College Of Rheumatology/European League against Rheumatism)

- **關節發炎的數量與部位**
  - 2-10個大關節(從肩肘髖膝踝的關節)→1分
  - 1-3個小關節(從掌指關節之間、近端指間關節、第二至第五蹠趾關節、拇指、手腕間關節)→2分
  - 4-10個小關節→3分
  - 大於10個關節(至少要有1個小關節)→5分
- **血清學異常-Rheumatoid factor (RF)或 anti-citrullinated peptide/protein antibody (ACPA)**
  - RF或ACPA兩項中有一項高於正常值，但數值低於正常值的3倍→2分
  - RF或ACPA兩項中有一項高於正常值，且數值高於正常值的3倍→3分
- **抽血檢驗發炎指數：CRP或ESR於正常值的上限→1分**
- **症狀持續六週以上→1分**

若病人總分達到6分以上(總分10分)，即可確診為類風濕性關節炎

疾病嚴重度評估工具：ACR Responses criteria & DAS28

- **ACR Responses criteria** ：美國風濕病學會所製定的標準，分為ACR20、ACR50、ACR70。ACR20 定義為病人腫脹及觸痛關節數(28個)有20%改善，以及下列五項中至少有三項改善20%以上：患者對疼痛的評估、患者的綜合評估、醫生的綜合評估、患者對活動能力的自我評估、發炎指數(CRP或ESR)。

- **DAS 28 (Disease Activity Score 28)**：主要是評估28處關節疾病活動度，主要是依據四項指標來決定DAS28的數值。下列為四項指標：
  - ✓TJC28 (Tender Joint count)：28個關節中有觸痛關節數
  - ✓SJC28 (Swollen Joint count)：28個關節中有腫脹關節數
  - ✓ESR：紅血球沉降速率
  - ✓GH (general health)：整體健康狀態評估

藥物治療

- 抗發炎藥物（非類固醇類）：Cox-2 selective NSAID
- 調發疾病緩解之免疫抑制藥物
  - 傳統藥物
    - 抗瘧疾藥物Hydroxychloroquine（Plaquenil）、Sulfasalazine（Salazopyrin）、Azathioprine（Imuran）、環孢素Cyclosporin（Neoral）、Leflunomide（Arava）、Cyclophosphamide（Cytoxan）
  - 生物製劑
    - 抗腫瘤壞死因子藥物 Etanercept（Enbrel）
    - 復邁 Adalimumab（Humira）
    - 莫維達（MabThera）
    - Anakinra（Kineret）
    - IL-6 monoclonal Ab
- 類固醇、關節內注射類固醇

SCENARIO

一位60歲女性患者，具類風溼性關節炎病史，持續門診追蹤治療已20年，她曾接受DMARDS，Immunotherapy，與Steroid等治療方式，但病情反覆，效果不如預期。

患者來到中醫就診，詢問醫師：「**雷公藤**對於類風溼性關節炎是否有療效？要吃到多少才會改善類風濕性關節炎的症狀呢？」

執行實證醫學五大步驟

- 提出問題(Ask: PICO)
  - Formulate an answerable question
- 搜尋證據(Acquire)
  - Track down the best evidence
- 嚴格評讀(Appraisal: VIP)
  - Critically appraise the evidence
- 恰當應用(Apply: 3E)
  - Integrate with clinical expertise and patient values
- 評估結果(Audit)
  - Monitoring your performance

ASK(PICO)- Asking an Answerable Clinical Question

PICO	
Problem 病人問題	Rheumatoid Arthritis
Intervention 介入處置	*Tripterygium wilfordii* Hook F
Comparison 對照處置	Standard pharmacological treatment (ST)
Outcome 臨床結果	swollen joint count(SJC); duration of morning stiffness(DMS); grip strength(GS); rheumatoid factor(RF); erythrocyte sedimentation rate(ESR)

ACQUIRE- Searching The Best Evidence

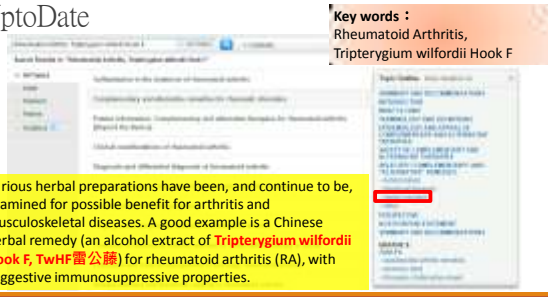
Model of Organization of EBM Information Study

Level of evidence	Grading criteria	Grade of recommendation
1a	Systematic review of RCTs including meta-analysis	A
1b	Individual RCT with narrow confidence interval	A
1c	All or none studies	B
2a	Systematic review of cohort studies	B
2b	Individual cohort study and low quality RCT	B
2c	Outcome research study	C
3a	Systematic review of case-control studies	C
3b	Individual case-control study	C
4	Case series, poor quality cohort and case control studies	C
5	Expert opinion	D

RCT = Randomized controlled trial.

UptoDate

Key words：
Rheumatoid Arthritis,
Tripterygium wilfordii Hook F



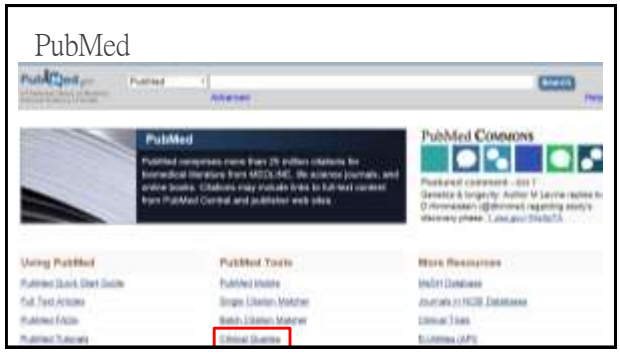
Various herbal preparations have been, and continue to be, examined for possible benefit for arthritis and musculoskeletal diseases. A good example is a Chinese herbal remedy (an alcohol extract of **Tripterygium wilfordii Hook F, TwHF雷公藤**) for rheumatoid arthritis (RA), with suggestive immunosuppressive properties.

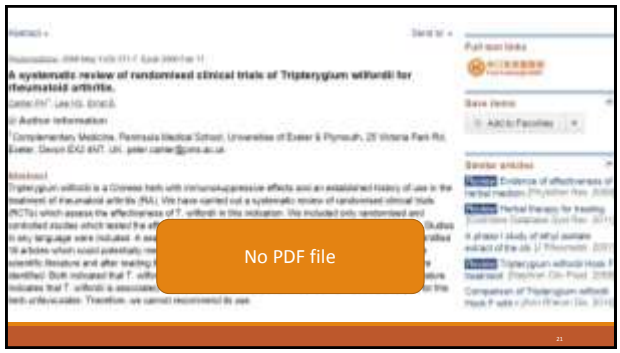
Dynamed

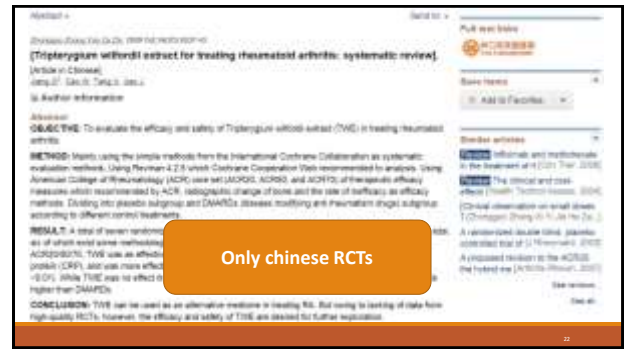
Key words：
Rheumatoid Arthritis,
Tripterygium wilfordii Hook F

RESULT:
無相關的文獻摘要

PubMed







APPRAISAL

- VIP
  - Validity
  - Impact
  - Practice Applicability
- **Oxford CEBM Critical Appraisal Sheets**
  1. 此篇系統回顧是否提出明確定義的問題？
  2. 是否此篇回顧的搜尋策略可能有遺漏可能合適的臨床試驗？
  3-1. 研究收錄標準是否有明確的界定？
  3-2. 關於研究族群、涉入治療、比較分組及結果評估是否適切？
  4. 所收錄的研究是否是有效力(valid)的研究（randomization, blinding and completeness of follow-up ）？
  5. 如果有**meta-analysis**，所收錄的研究是否有足夠的一致性以產生合併的資料？

1. 此篇系統回顧是否提出明確定義的問題？(PICO)

What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The *Title, Abstract* or final paragraph of the *Introduction* should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes ☐ No ☐ Unclear ☐	

Problem 病人問題，Intervention 介入處置，Comparison 對照處置，Outcome 臨床結果

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- Title

Intervention

Extracts of *Tripterygium wilfordii* Hook F in the Treatment of Rheumatoid Arthritis: A Systemic Review and Meta-Analysis of Randomised Controlled Trials

Problem

- Abstract

Comparison

Randomised controlled trials (RCTs) comparing the effects of *Tripterygium wilfordii* Hook F (TwHF) extracts (TEs) and placebo (PBO) or disease-modifying antirheumatic drugs (DMARDs) in patients with RA were included.

Compared with DMARDs, TEs alone produced a mild increase in [illegible] (GS).

☑ Yes
☐ No

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2. 此篇回顧的搜尋策略是否可能遺漏可能合適的臨床試驗？

F - Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g. Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The **Methods** section should describe the search strategy, including the terms used, in some detail. The **Results** section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.
This paper: Yes ☐ No ☐ Unclear ☐	

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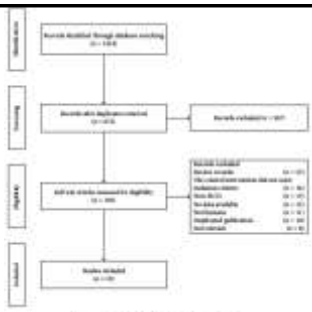
2.1. *Search Strategy.* We searched the following digital databases to identify trials: PubMed, Embase, the Cochrane Library, and Clinical Trials.gov. In addition, we searched the Chinese databases, such as the CNKI Database, VIP Database, CBM Database, WanFang Database, and Chinese Clinical Trial Register. All of the databases were searched from their available dates of inception to the latest issue (January 2013).

Different search strategies were combined as follows. For the English databases, we used free text terms, such as "*Tripterygium wilfordii* Hook F," "lei gong teng," "thunder god vine," or "yellow vine" (which are all alternative names in Chinese for *Tripterygium wilfordii* Hook F) and "rheumatoid arthritis," or "RA." For the Chinese databases, free text terms were used, such as "lei gong teng" or "huang teng" (which means *Tripterygium wilfordii* Hook F in Chinese) and "lei feng shi guan ite yan" (which means rheumatoid arthritis in Chinese). A filter for clinical trials was applied. To collect an adequate number of trials, the reference lists of relevant publications were also searched to identify additional studies.

明確指出**搜尋方式**及**關鍵字**，且**未受到語言限制**，有**明確Mesh term**



有註明**回顧論文總數量及排除數量及原因**

☑ Yes
☐ No

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3-1.研究收錄標準是否有明確的界定？

A - Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The **Methods** section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes ☐ No ☐ Unclear ☐	

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Inclusion Criteria

Randomised controlled trials (RCTs) were included regardless of blinding, publication status, or language. Studies were selected for analysis if they satisfied the following criteria:
(1) the subjects took extracts of TwHF alone or with other DMARDs for at least 4 weeks
(2) the study was an RCT with a parallel or crossover design
(3) TEs were used as an active treatment intervention
(4) people enrolled were diagnosed with RA, according to the 1987 guidelines of the American Rheumatology Association.

Exclusion Criteria

(1) studies using any TwHF-containing herbs or other herbal extracts were excluded.
(2) Case reports, reviews, retrospective studies, or studies without control groups were also excluded.
(3) Studies were also excluded if the dose of TEs was not available.
(4) RCTs that lacked sufficient data to allow for the calculation of the net changes in outcomes and their variances from the baseline to the endpoint were also eliminated fro more analysis.

3-2.關於研究族群、涉入治療、比較分組及結果評估是否適切？

Study Groups

10RCTs(9 in China, 1 in USA)

Intervention

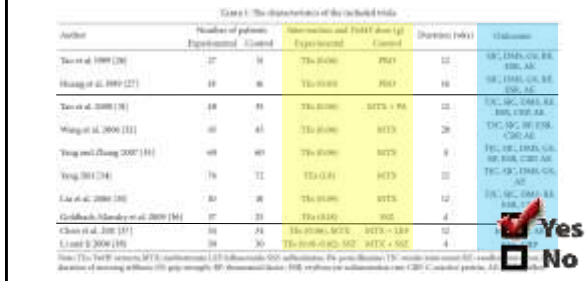
TEs compared with a placebo(PBO); TEs compared with DMARDs; and TEs with DMARDs compared with DMARDs alone.

Groups comparisons

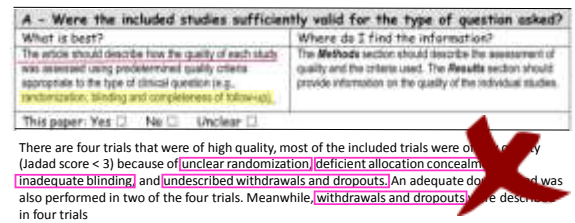
Two studies compared TEs with a PBO.
Six studies randomised the participants to receive TEs alone versus a control of DMARDs.
Two trials compared a cointervention of TEs and DMARDs (methotrexate, or sulfasalazine) with a control of DMARDs alone.

Outcomes

The primary outcomes were tender joint count (TJC), swollen joint count (SJC), duration of morning stiffness (DMS), and grip strength (GS).
The secondary outcomes consisted of rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

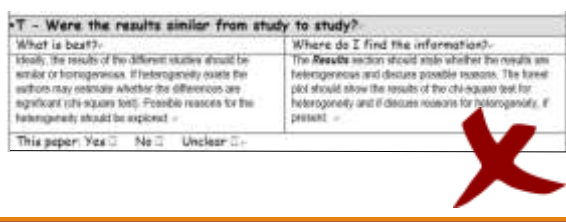


4.所收錄的研究是否為有效力(valid)的研究？

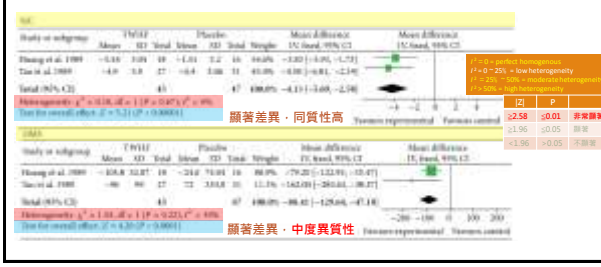


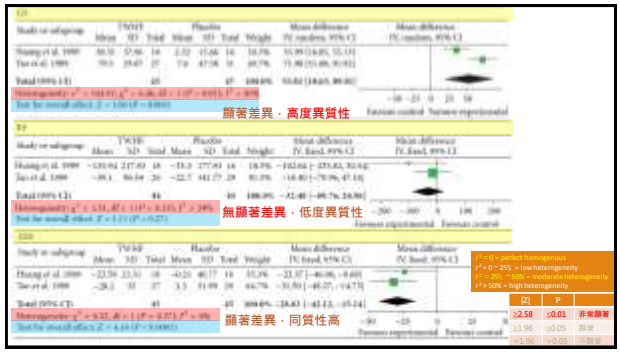
There are four trials that were of high quality, most of the included trials were o… (Jadad score < 3) because of unclear randomization, deficient allocation concealm… inadequate blinding, and undescribed withdrawals and dropouts. An adequate do… was also performed in two of the four trials. Meanwhile, withdrawals and dropouts … in four trials

5.如果有meta-analysis，所收錄的研究是否有足夠的一致性以產生合併的資料？



TEs compared with a PBO

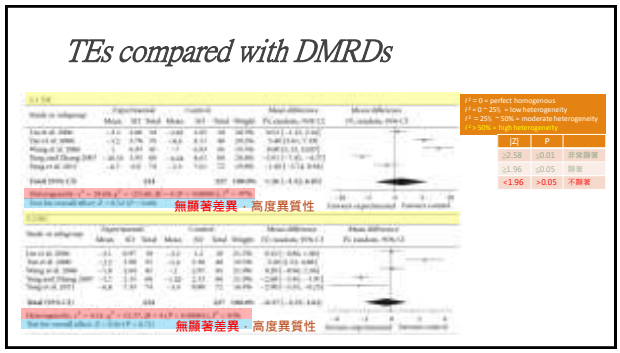


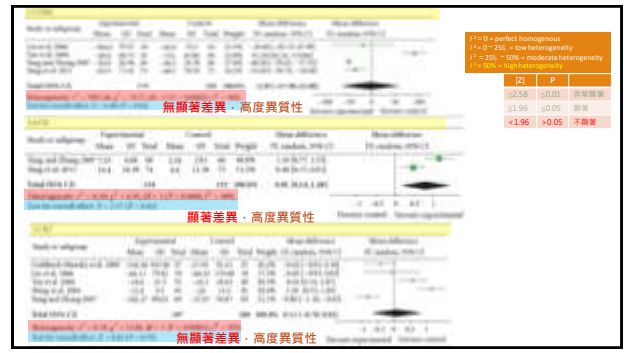


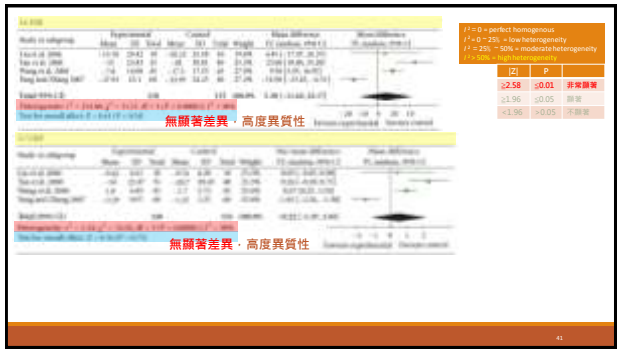
- The significant difference was identified between TEs and PBO in terms of the **SJC**, **DMS**, and **ESR**.
- A small but significant increase in **GS** was also found.

TEs were superior to PBO in improving joint function and reducing disease activity in RA.

TEs compared with DMRDs







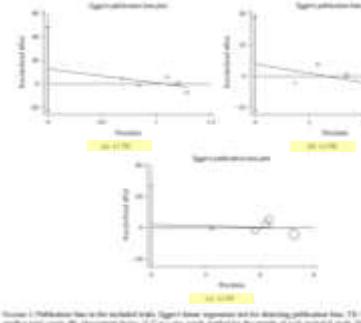
- The pooled results displayed no significant differences between TE-treated group and the DMARDs group, aside from GS.
- However, no effects were found for TJC, SJC, DMS, RF, ESR ,or CRP.
- Only one trial described the results, which were a 20% improvement in RA as defined by ACR (ACR 20), ACR50, and ACR70, so we did not pool these results.

There were no beneficial effects on SJC,DMS,or ESR when comparing Tes with DMARDs. Furthermore, the TE group had increased GS compared with the DMARDs group.

TEs with DMARDs compared with DMARDs

- The statistical heterogeneity among the studies was found to be significant regarding the results for ESR(P= 0.05).
- The pooled results showed no significant differences between the two groups in terms of ESR or CRP.
- Unfortunately, none of the included trials reported its results: ACR 20, ACR 50, or ACR70.

TEs plus DMARDs had the same effects as those of two synthetic DMARDs alone in terms of lowering disease activity in RA.



Egger'spublication bias plots and Begg's test showed that there were **no significant publication biases** for three outcomes in which the numbers of the included trials were not less than 5.
However, these results cannot be considered convincing because there were fewer than ten trials.

AEs

- 7 reported mild to moderate gastro-intestinal events in a few of the participants who received TEs.
- Menstruation disorders or amenorrhea was reported in 6 trials in the TE group.
- 3 trials reported mild liver function abnormalities in a few patients caused by the intake of TEs.

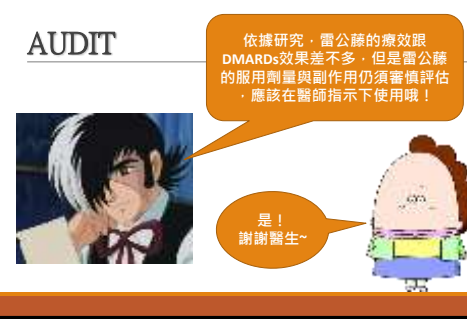
Due to different interventions,limited data, and the lowquality of the included studies,the Aes were not ultimately combined.

APPLY

3E：evidence, experience, expectation

我們的病人是否與研究中差異很大	同樣是RA患者
您期望您的病人從研究結果中獲得多大的好處？	病人可服用雷公藤使類風濕性關節炎獲得改善
還有哪些替代方案？	Glucocorticoids, DMARDs, Biologic DMARDs
研究結果適用於您的病人嗎？	不一定
我們的病人如何看待此治療的結果	可參考

AUDIT



THANKS FOR Ur ATTENTION