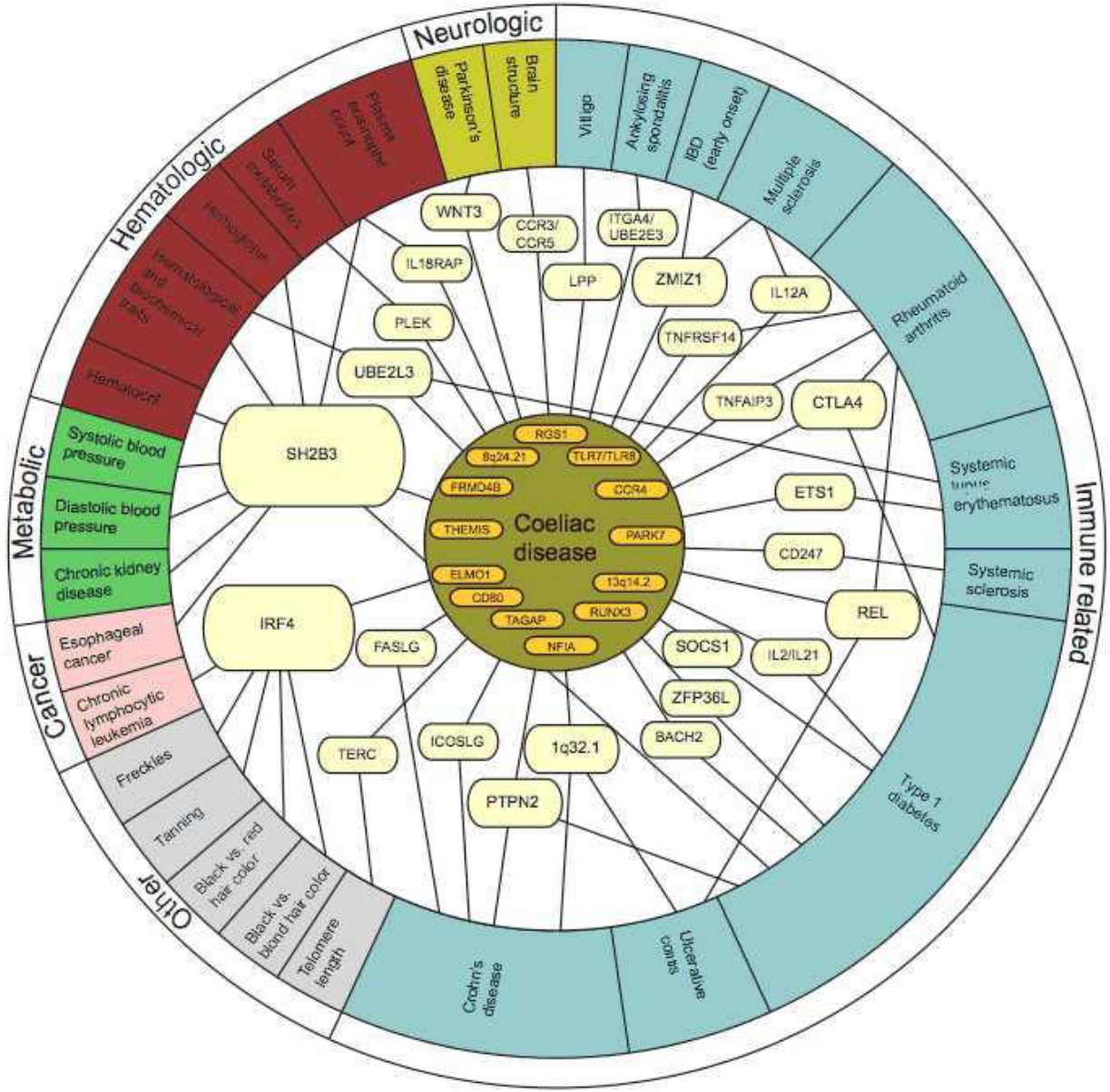
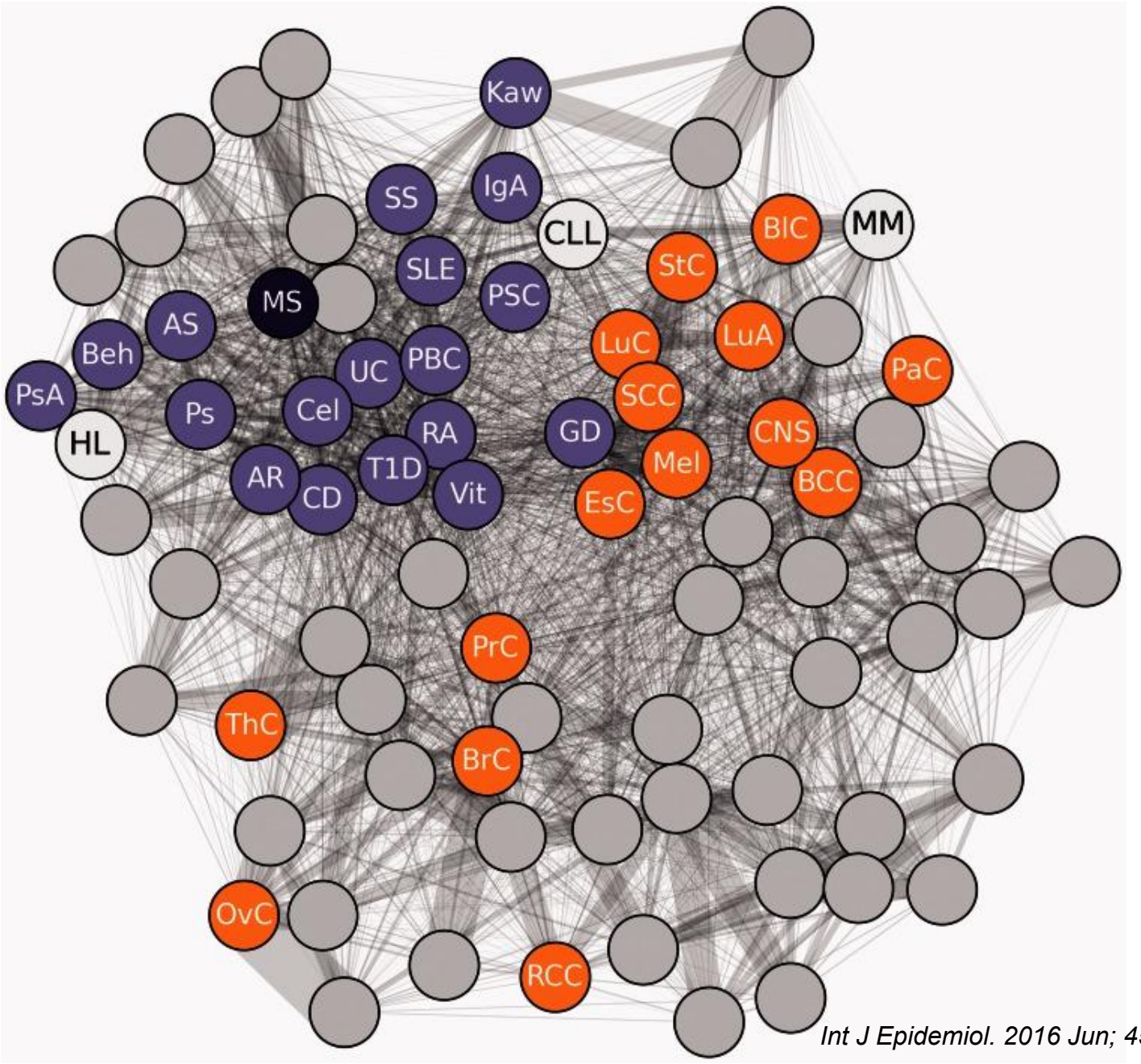
艾拉莫德临床应用

仁济S风湿
叶霜

免疫炎性疾病的共同机制



免疫炎性疾病机制相关性



Int J Epidemiol. 2016 Jun; 45(3): 728–740.

RA的治疗选择

传统DMARDs
- 甲氨蝶呤
- 艾拉莫德
- 来氟米特
- 羟氯喹
- 柳氮磺胺吡啶
- 雷公藤

外科手术

- 一般治疗
- 关节制动(急性期)
- 关节功能锻炼
- 物理疗法等

RA的达标治疗

RA达标治疗层次

症状学

影像学

免疫学

生物制剂DMARDs
- TNFα拮抗剂
- 抗CD20单抗
- CTLA4
- IL-6抑制剂

糖皮质激素
NSAIDs

小分子酶抑制剂
- JAK抑制剂

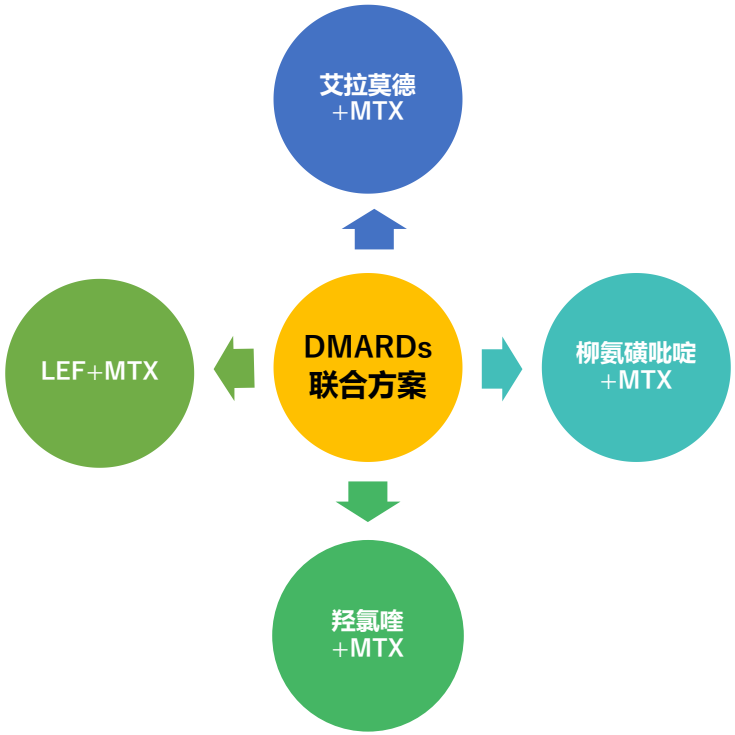
1.Yazici,et al,Arthritis Rheumatol. 2016 May;68(5):1315-6
2. APLAR rheumatoid arthritis treatment recommendations, Int J Rheum Dis. 2015 Sep;18(7):685-713

艾拉莫德作为传统DMARDs的特点

	艾拉莫德	来氟米特	MTX
T淋巴细胞	影响较小	抑制T淋巴细胞增殖	促进T淋巴细胞凋亡
B淋巴细胞	明显抑制，作用强于LEF和MTX	抑制，但不明显	无明显抑制
成骨细胞	促进成骨细胞分化	无明显作用	抑制成骨细胞分化
破骨细胞	抑制破骨细胞生成，不影响细胞增殖	抑制破骨细胞生成，影响细胞增殖	抑制破骨细胞生成，影响细胞增殖
CIA炎症	明显抑制	明显抑制	明显抑制
MMP-1 MMP-3	明显抑制	促进MMP-1和MMP-3	抑制
IL-17	明显抑制	无明显作用	无明显作用

传统DMARDs联合用药在RA治疗中的作用

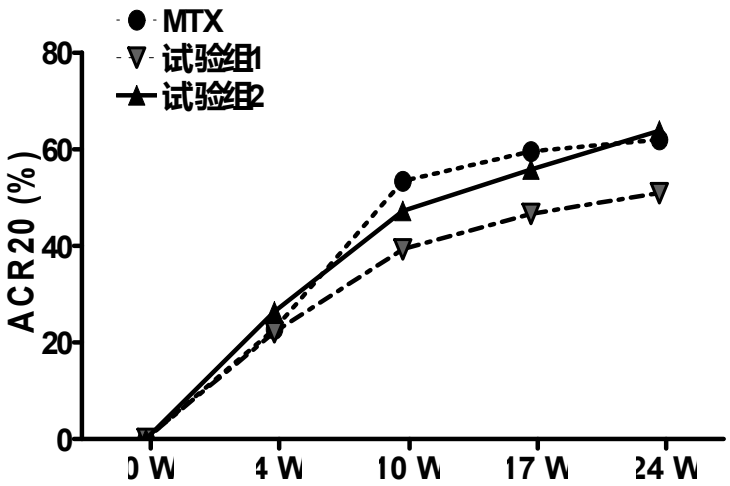
- DMARDs单药治疗仍然是中/高疾病活动度的患者，推荐给予DMARDs联合治疗;
- 艾拉莫德+MTX是一个可供选择的联合治疗方案.



1. Singh, et al, Arthritis Rheumatol, 2016, 68(1):1-26
2. Naoki, etal, ModRheumatol, 2013, 23:430-439

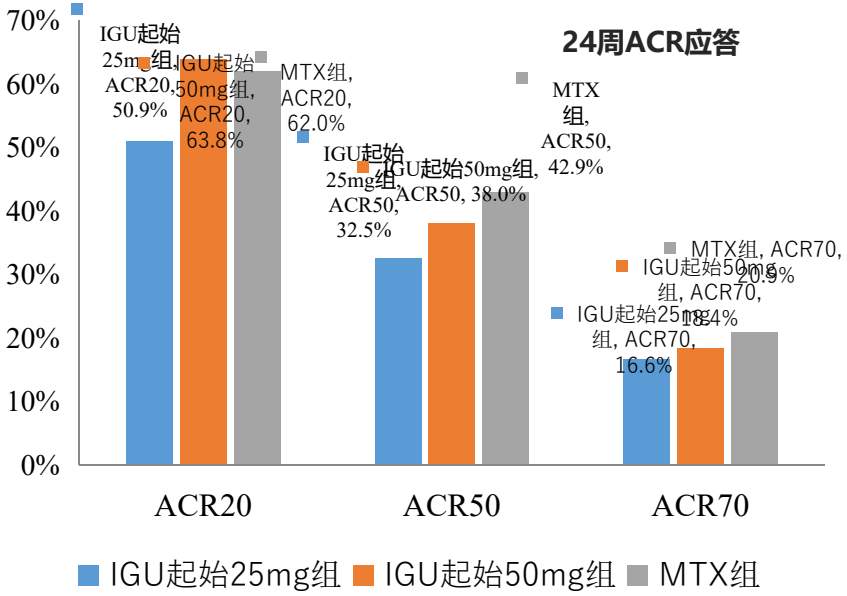
艾拉莫德单药治疗疗效与MTX相当

●III期临床研究显示：24周终点时艾拉莫德起始50mg/d组的ACR20显著优于艾拉莫德 起始4周25mg/d后50mg/天组，与MTX组相近.



MTX组 ： 起始4周10mg/W，之后15mg/W
试验组1：起始4周艾拉莫德25mg/d，之后50mg/d
试验组2：艾拉莫德50mg/d

✓ 在24周终点时IGU50mg组ACR20非劣（非劣效界值为10%）于MTX

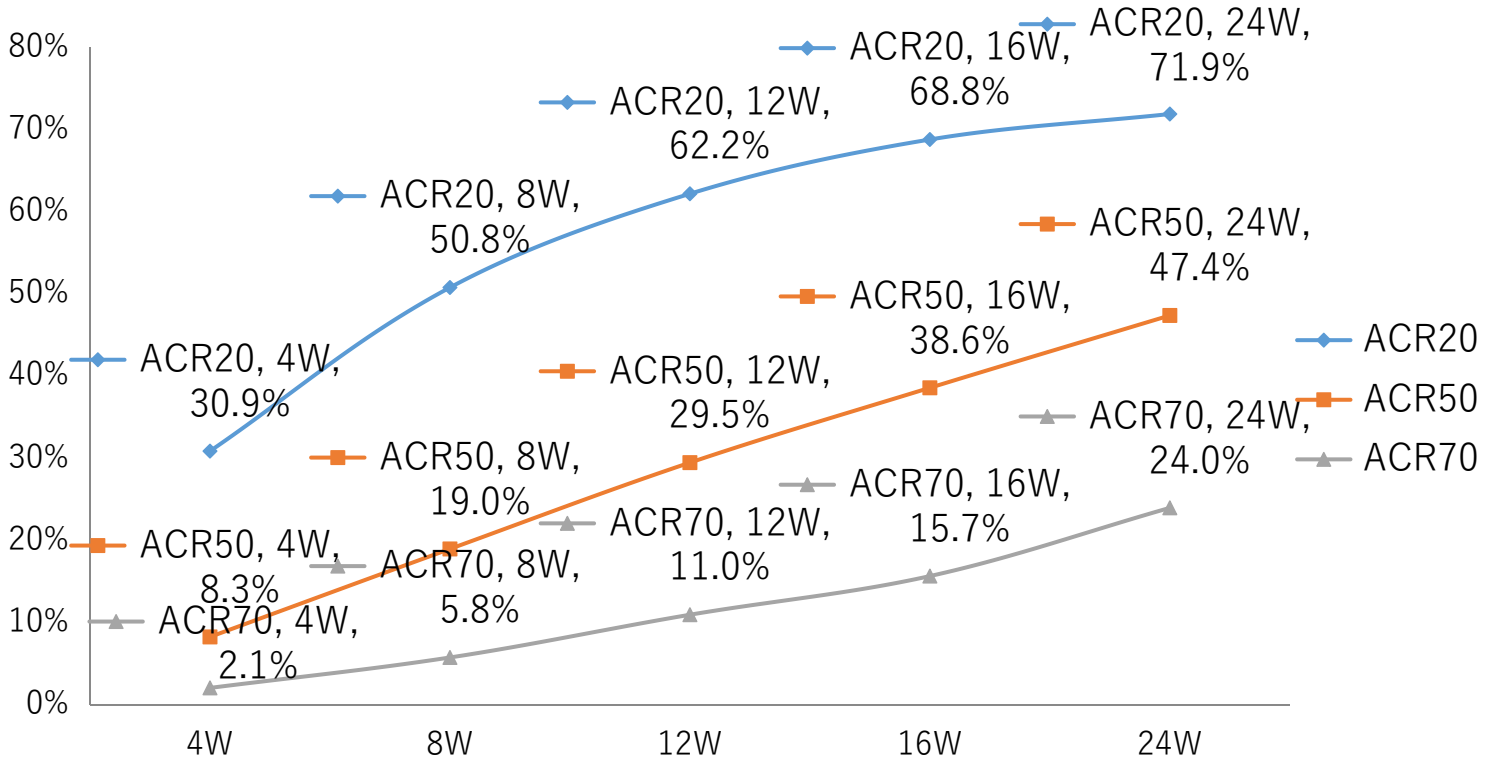


一项随机、双盲、对照临床研究，共纳入489例活动期RA患者，分别采用艾拉莫德前4周25mg/d后20周50mg/d(25mg/次，每天2次）、25mg/d(25mg/次，每天1次）和安慰剂治疗24周。主要终点为ACR20等.

Lü liang-jing,et al.Arthritis&Rheumatism(Arthritis Care&Research) 2009,121:979-987

长疗程使用艾拉莫德，患者改善比例显著递增

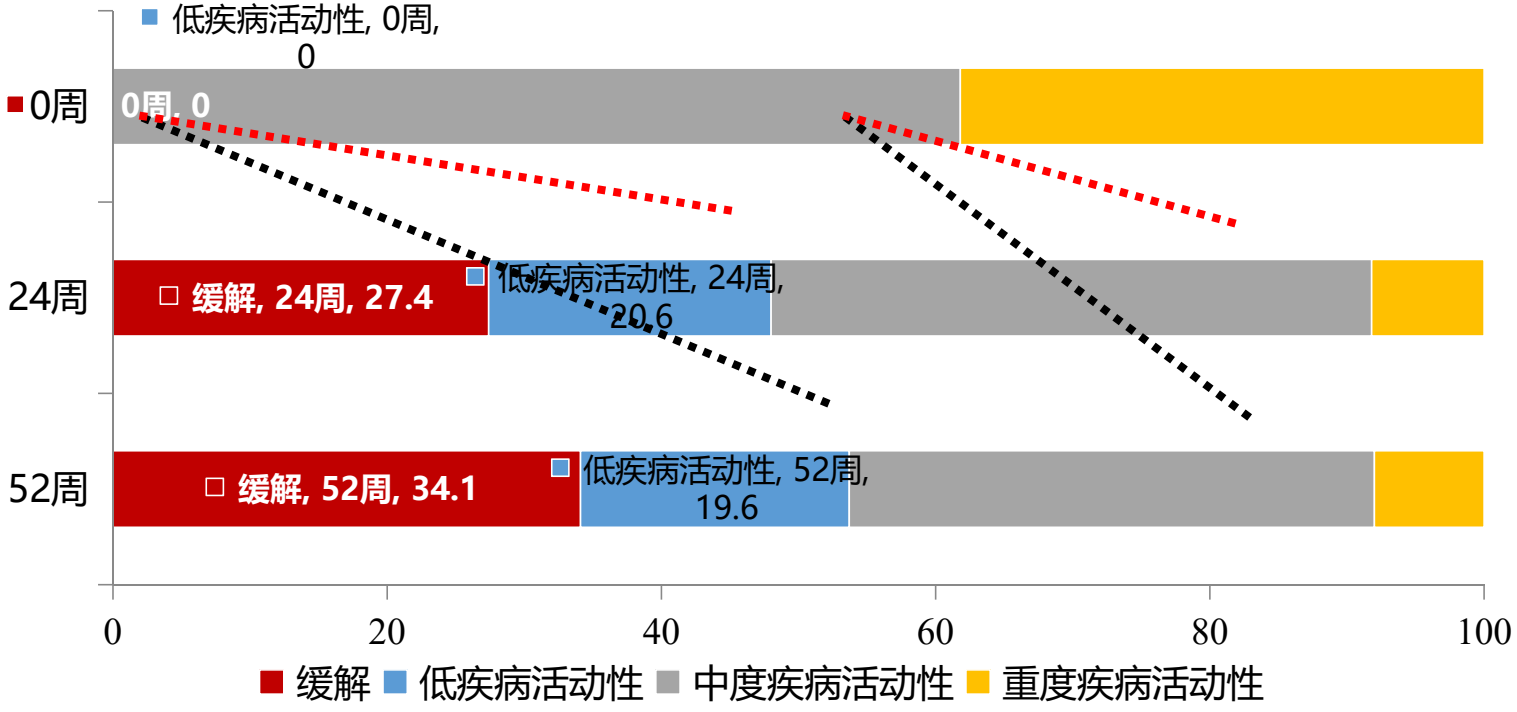
- **ACR20/50/70患者比例随着治疗时间延长持续增加**



●一项开放、单臂、多中心临床研究，共纳入1759例RA患者，饭后服用，每日早晚各服1片（25mg），主要终点：疗效指标：24周末ACR20、ACR50、ACR70的比率；DAS28平均值较基线值（0周）的变化；临床缓解率；HAQ变化；情绪变化情况。安全性指标：治疗前、疗程中、治疗后体格检查和生命指征的变化（心率、心电图）以及实验室检查指标的变化；不良事件发生率和严重程度比较

艾拉莫德与MTX长期联用持续降低了患者的疾病活动度

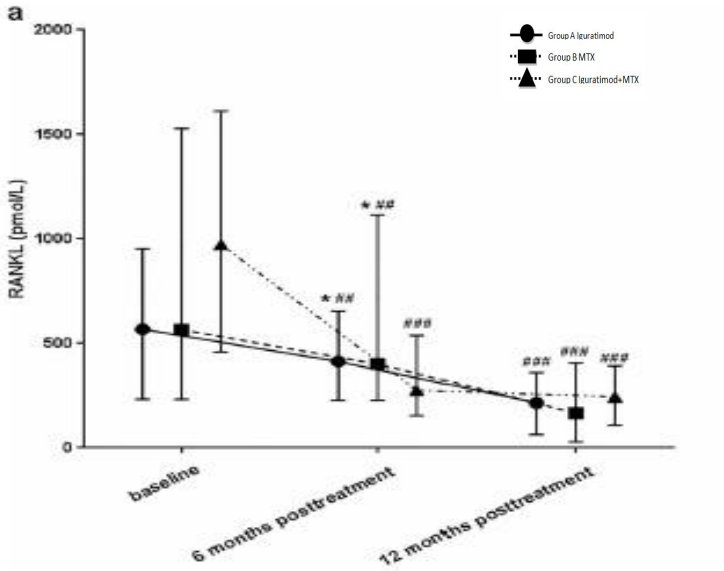
- 与0周相比，联用24、52周显著减少了重度疾病活动性的患者比例，提高了缓解和低疾病活动性的患者比例（P<0.001）
- 在缓解患者比例上，尽管52周和24周没有显著差异，但在数值上有所增加



艾拉莫德联用MTX 0、24和52周缓解、低、中和重度疾病活动性的患者百分比(%)

艾拉莫德可显著抑制RANKL的表达
延缓骨破坏的发生

●一项随机、双盲、对照临床研究，共纳入67例RA患者，随机分为3组：艾拉莫德组（n=21）25mg bid；甲氨蝶呤组（n=22）10mg QW；艾拉莫德+甲氨蝶呤（n=24）；随访12个月，主要终点：DAS28、RANKL、OPG、DKK-1、CTX-1等水平变化

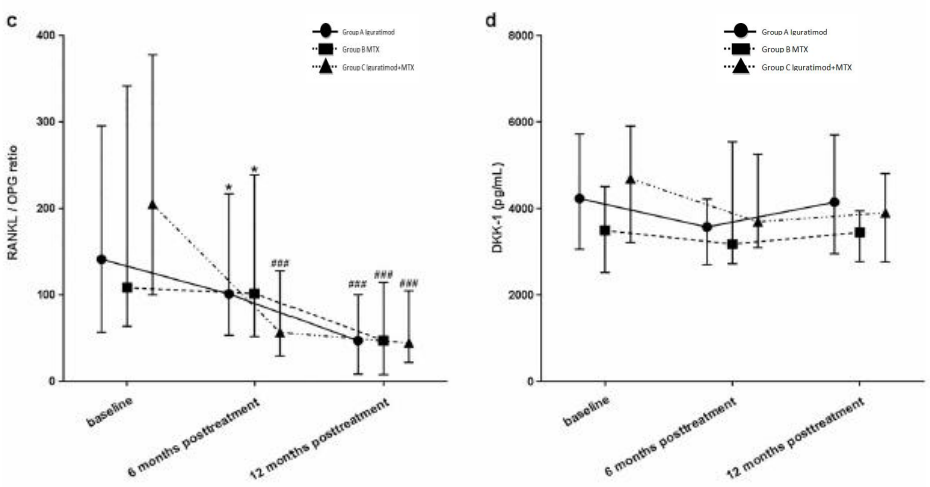


- 与基线相比，各组治疗后都显著抑制RANKL的表达，有效阻止骨侵蚀（p<0.001），但各组间无统计学意义（p>0.05）
- 治疗6月后（基线vs 6月）：艾拉莫德565pmol/L vs. 411pmol/L, p=0.002; MTX=562.5pmol/L vs. 399.5pmol/L, p=0.005; 艾拉莫德+MTX=971pmol/L vs. 272.5pmol/L, p<0.001
- 治疗12月（基线vs12月）: 艾拉莫德 565pmol/L vs.212pmol/L; MTX:562.5pmol/L vs.163.5pmol/L;艾拉莫德+MTX971pmol/L vs. 241.50pmol/L; p < 0.001）

Liqi Bi,et al, Clin Rheumatol (2017) 36:1369–1377

艾拉莫德显著改善RANKL/OPG比率水平，骨保护作用显著

●一项随机、双盲、对照临床研究，共纳入67例RA患者，随机分为3组：艾拉莫德组（n=21）25mg bid；甲氨蝶呤组（n=22）10mg QW；艾拉莫德+甲氨蝶呤（n=24）；随访12个月，主要终点：DAS28、RANKL、OPG、DKK-1、CTX-1等水平变化



- 与基线时相比，各组12月后RANKL/OPG比率显著下降，（$p<0.001$），但各组间无统计学意义（$p>0.05$）；治疗6月后，仅艾拉莫德+MTX组RANKL/OPG比率显著下降(基线vs.6月: 205.17vs. 56.76, $p< 0.001$)
- 治疗12月后，(基线vs12月:艾拉莫德组41.10vs.47.24;MTX组08.23vs47.34;艾拉莫德+MTX205.17vs44.56;$p<$ 0.001).

Liqi Bi,et al, Clin Rheumatol (2017) 36:1369–1377

兼具NSAIDs样作用，胃粘膜损伤不明显

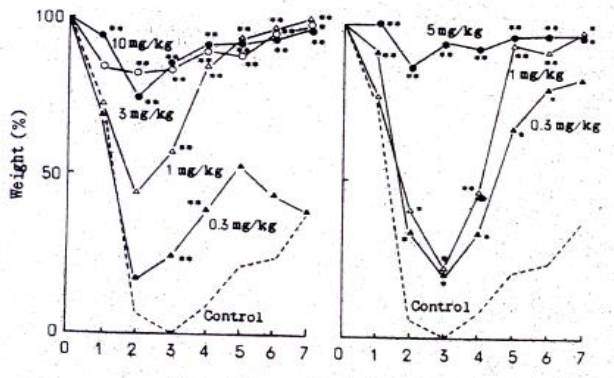


Fig. 9: Effect of T-614 *(left)* and indometacin *(right)* on the urate-induced knee joint pain in dogs. Each point represents the mean of the values obtained from 3—7 animals. Significant difference from control: * $p < 0.05$, ** $p < 0.01$.

镇痛

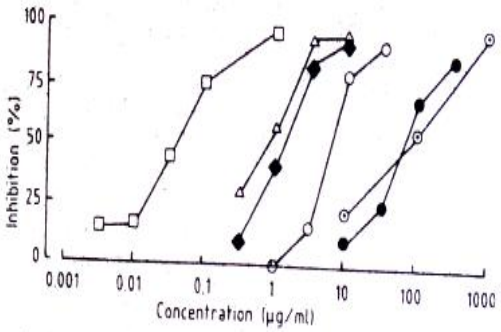


Fig. 1: Effect of T-614 and reference compounds on PGE_2 formation by rabbit renal medulla microsomes. Each point represents the mean value of the percent inhibition obtained from 2—4 separate experiments. ● T-614, ○ nimesulide; □ indometacin; △ ibuprofen; ⊙ ASA; ◆ AMTP. Convertion rate from arachidonic acid to PGE_2 in the control was 11.0 ± 1.0 % (mean with S.E., n = 6).

抑制PGE2是吲哚美辛的1/20，
与Asp相当Cox2特异
胃粘膜损伤不明显

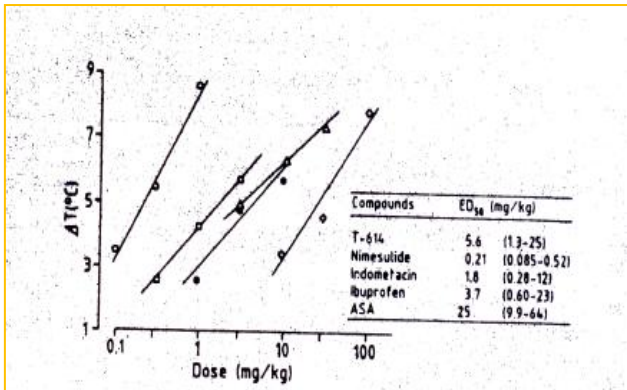
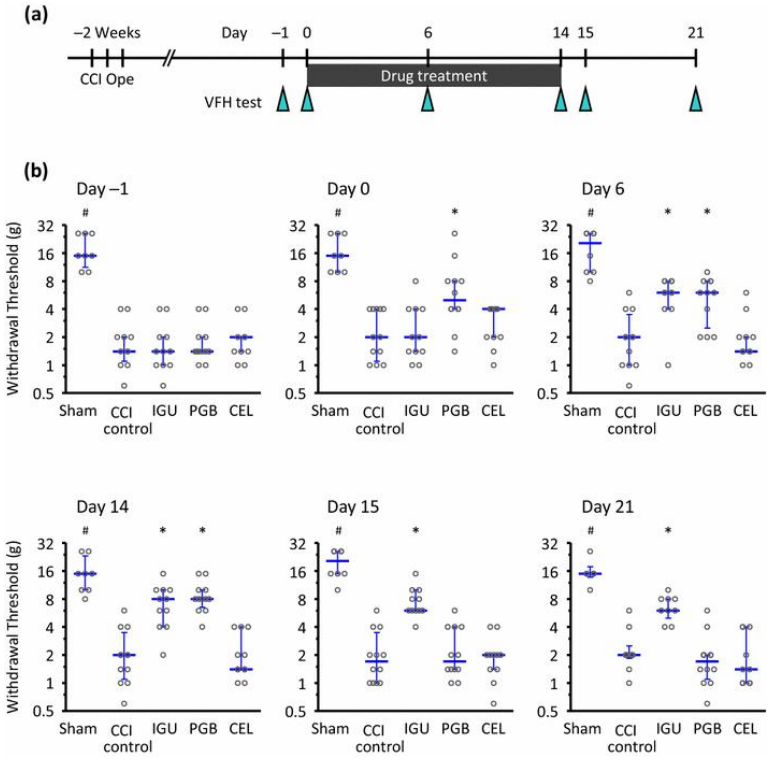
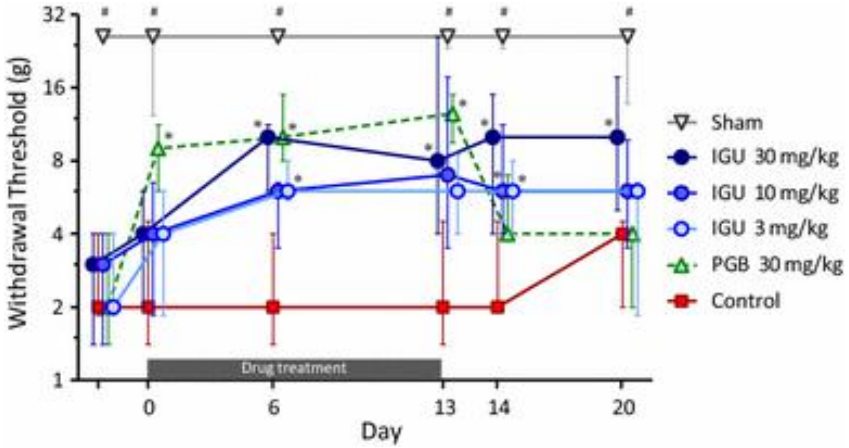


Fig. 10: Antipyretic effect of T-614 and reference compounds on the yeast-induced fever in rats. Each point represents the mean of the values obtained from 6—8 animals. ● T-614, ○ nimesulide, □ indometacin, △ ibuprofen, ◇ ASA. ED_{30} was defined as the dose necessary for causing a Δ T °C by 5. The figures in parentheses represent 95 % confidence limits.

镇痛

艾拉莫德具有多模式止痛作用

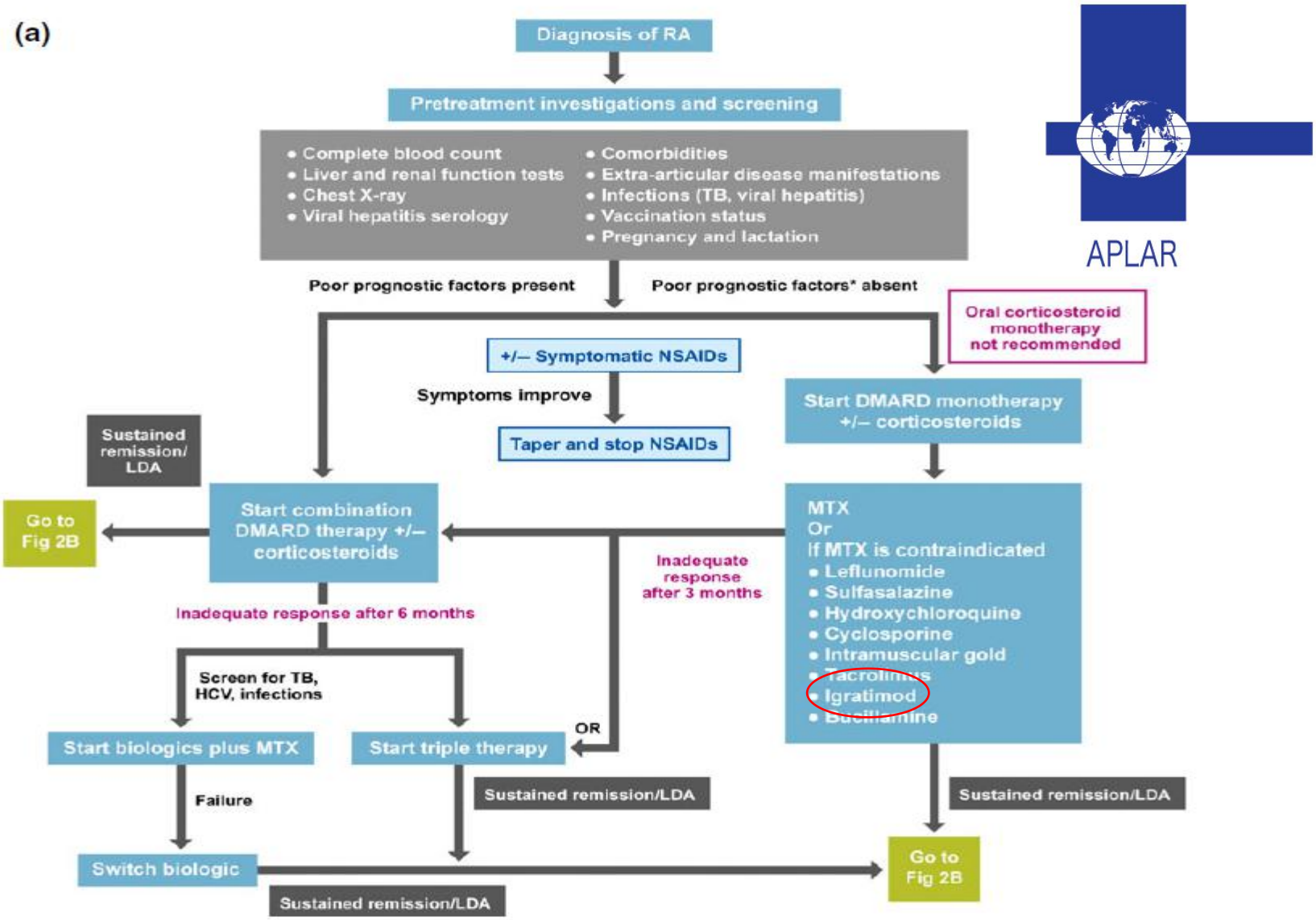




Effects of iguratimod (IGU), pregabalin (PGB) and celecoxib (CEL)on chronic constriction injury (CCI)-induced static allodynia in rats

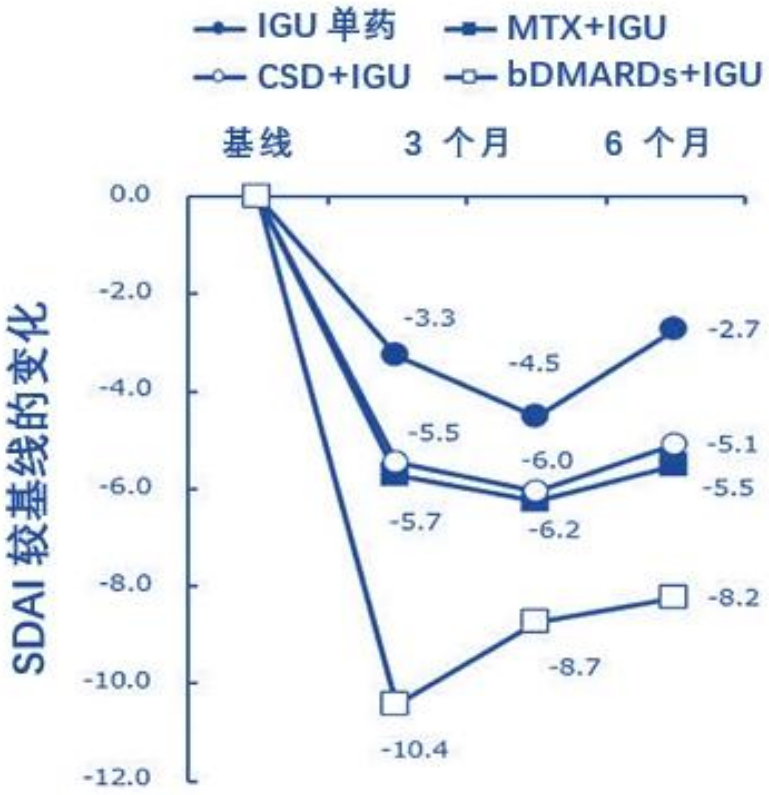
Inflamm Res. 2017 Oct;66(10):855-862.

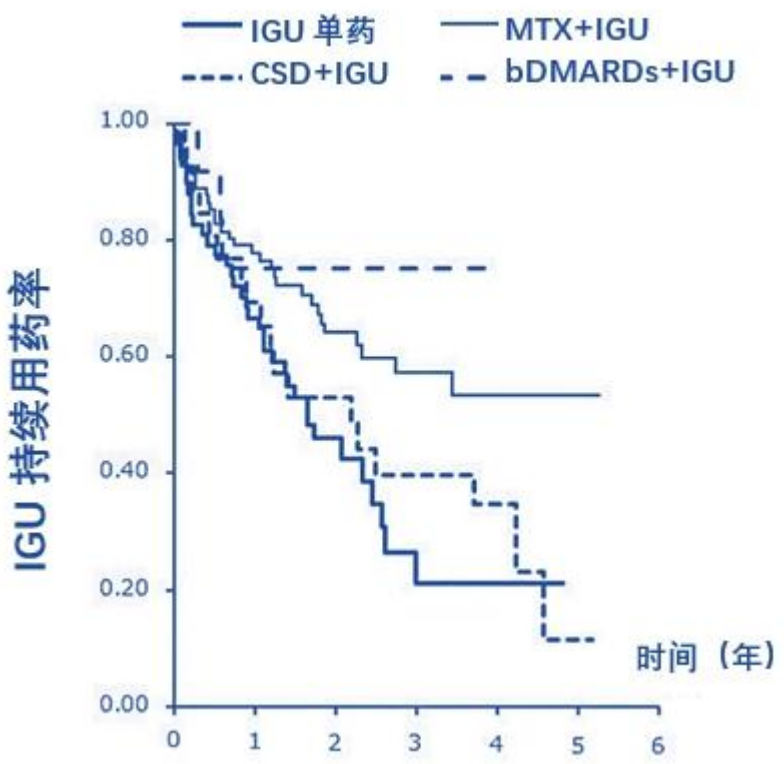
2014年艾拉莫德纳入APLAR指南



2019 EULAR

- 日本研究者Yukiyoshi Oishi等人基于真实世界的数据， 研究回顾了2013年4月至2017年6月间接受IGU治疗的178例RA患者的数据。根据用药情况将患者分为4组：
- （1）IGU单药组（n=59）； （2）MTX+IGU组（n=81）； （3）CSD+IGU组（n=26）[CSD=除MTX外的csDMARDs：柳氮磺胺吡啶、他克莫司、布西拉明]； （4）bDMARDs+IGU组（n=12）。
- 基线时，IGU单药组，MTX+IGU组，CSD+IGU组和bDMARDs+IGU组的SDAI水平分别为：14.2, 12.8, 21.3和18.4。IGU治疗后，4组患者的SDAI均获得显著改善。一年时，各组SDAI较基线的变化值无显著差异。提示无论何种IGU疗法均可获得较好疗效。





艾拉莫德可能拓展应用领域

◆关节炎

类风湿关节炎

强直性脊柱炎

银屑病性关节炎

炎性肠病关节炎

骨关节炎

反应性关节炎

◆皮肤病血液炎性肠病

银屑病

皮肤型血管炎

结节性红斑

克隆氏病

溃疡性结肠炎

B细胞增殖性疾病

◆系统性自身免疫性疾病

干燥综合征

系统性红斑狼疮

硬皮病

多肌炎/皮肌炎

未分化结缔组织病

白塞病

抗磷脂综合征

◆器官特异性自身免疫性疾病

间质性肺病

肺动脉高压

IgG4相关疾病？

亚甲炎？

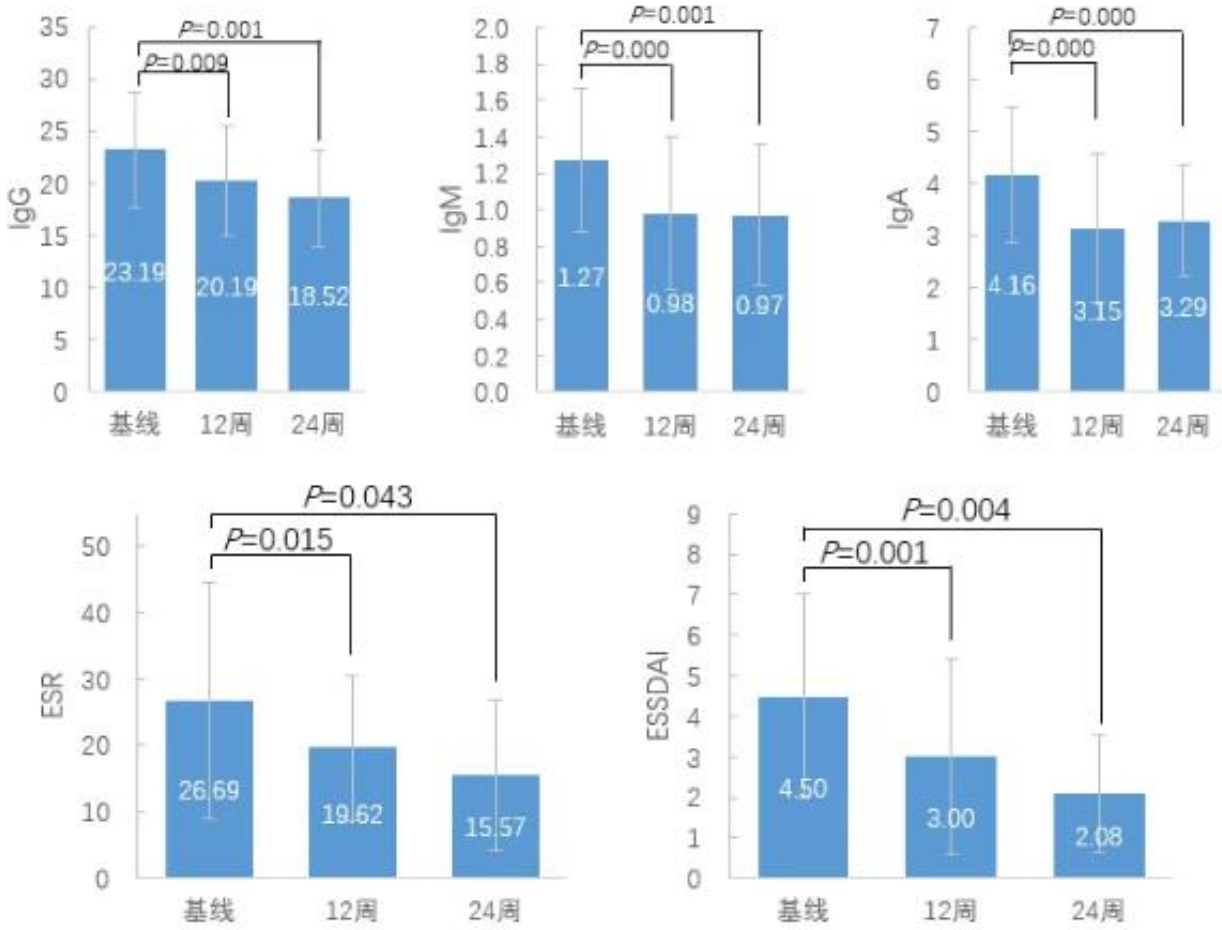
结节病？

木村病？

骨质疏松症？

2019 eular：艾拉莫德治疗原发性干燥综合征

北京大学人民医院临床免疫中心栗占国主任团队进一步报告了IGU对pSS的有效性及安全性[1]，该研究是中华国际医学交流基金会咨询项目（PANDA，编号：Z-2014-06-2-1636）。研究纳入21例pSS患者，均不伴有需激素治疗的严重系统损伤。给予IGU 25mg Bid治疗24周。共18例完成随访，经IGU治疗后，患者的ESSDAI评分，高球蛋白血症、血沉均较基线显著下降。



艾拉莫德治疗干燥综合征：思考

1、口眼干

2、腮腺肿

3、高球蛋白血症紫癜

4、关节炎

5、间质性肺炎

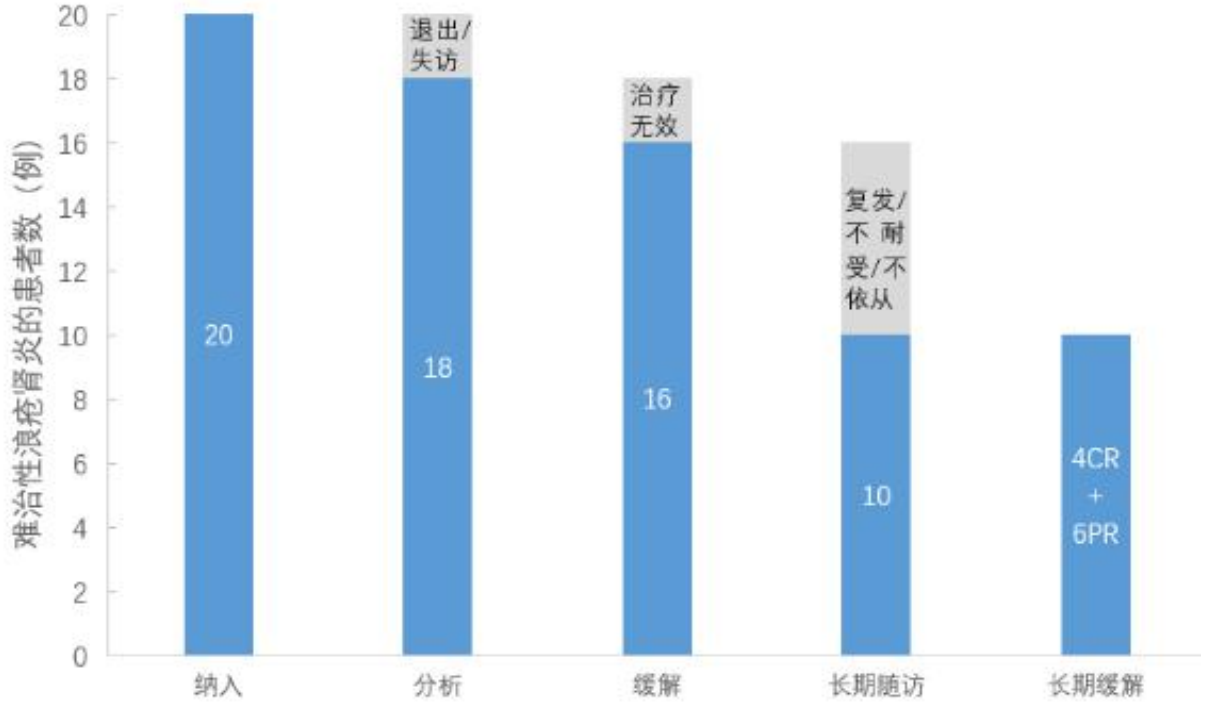
6、PBC

7、血液系统

8、肾小管酸中毒

2019 EULAR：艾拉莫德-难治性狼疮肾炎（LN）

- 上海交通大学医学院附属仁济医院风湿免疫科鲍春德主任团队，20例成人难治性LN患者入组（难治性LN的定义：入组前患者至少经历过两次治疗失败或复发；治疗失败指患者对某种免疫抑制剂无反应≥6个月），将原治疗方案中的免疫抑制剂调整为艾拉莫德（25mg Bid），其它治疗药物不变。20例难治性LN患者中女性18例，男性2例。基线时患者的中位尿蛋白水平为2.588 g/24h（0.98-13.79 g/24h），无显著肾外脏器受累，LN（III -V）。泼尼松中位使用剂量为10mg/d（5-35mg/d）。
- 共18例患者完成研究，其中16例达到部分缓解（PR）或完全缓解（CR）。有10例患者坚持了长期随访，中位随访时间为84周（28-144周），其中4例达到CR，6例达到PR。中位缓解时间为12周。



艾拉莫德治疗脊柱关节炎依据

1、IL-17是介导脊柱关节炎的重要炎症因子

2、外周关节炎、肌腱附着点炎：艾拉莫德/柳氮+MTX

3、中轴型：？

Scand J Rheumatol 2018;00:1–3

LETTER

Is iguratimod effective in refractory axial spondyloarthritis?

Y Luo, N Zheng, R Wu

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Iguratimod, also called T-614, is a novel small-molecular disease-modifying anti-rheumatic drug (DMARD) with anti-inflammatory actions. It was recommended for the treatment of rheumatoid arthritis (RA) at the 2012 European League Against Rheumatism (EULAR) meeting and in the 2014 Asia Pacific League of Associations for Rheumatology (APLAR) guideline (1). However, T-614 has a similar pharmacological profile to non-steroidal anti-inflammatory drugs (NSAIDs) (2) and also has inhibitory effects on cyclooxygenase (COX) and prostaglandin E_2 (PGE_2) (3). Axial spondyloarthritis (axSpA) is a chronic, autoinflammatory disease predominantly affecting the sacroiliac joints and spine. NSAIDs are effective for back pain, inflammation, and radiographic progression of the spine in axSpA, and are recommended as the first line treatment for axSpA (4). A few studies have shown the efficacy and safety of T-614 in the treatment of spondyloarthritis (SpA), with limited evidence from small sample data (5, 6). Considering the possibility of the effects and potential mechanism of T-614 in axSpA, we treated 17 refractory axSpA patients with T-614 for 12 weeks. We would like to share our experience of using T-614 in the treatment of refractory axSpA.

Seventeen patients with axSpA were treated at the First Affiliated Hospital of Nanchang University from October 2015 to June 2016. Ethical approval was obtained from the local research ethics committee at the First Affiliated Hospital of Nanchang University (number 330 006). All of the patients met the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA. These patients had high disease activity, defined as an Ankylosing Spondylitis Disease Activity Score (ASDAS) > 2.1 or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) > 4.0 (7), and had failed therapy on 2 weeks of NSAIDs. A stable dose of T-614 (25 mg, twice daily, orally; daily cost 35 CNY, ~USD 5.26) was given for the next 12 weeks. An evaluation of disease activity with BASDAI, ASDAS, patient's global assessment of disease activity (PGA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level was conducted once every month. Treatment response was assessed with the ASAS20, ASAS40, and BASDAI50 response criteria (8). Patients' characteristics at baseline are shown in Table 1. The 17 patients had a mean age of 49.8 ± 12.8 years and male-to-female ratio of 6:11. Eight patients dropped out owing to adverse effects (Table 2). Nine patients completed 3 months of T-614 therapy and two patients achieved complete remission. After 12 weeks of T-614 treatment, six (66.7%), four (44.4%), and three (30%) patients met the ASAS20, ASAS40, and BASDAI50 response criteria. The mean BASDAI scores decreased from 3.57 to 2.87, with a significant difference ($p < 0.05$). The percentage of patients achieving ASDAS-CRP < 1.3, 1.3 ≤ ASDAS-CRP ≤ 2.1, 2.1 ≤ ASDAS-CRP ≤ 3.5, and ASDAS-CRP > 3.5 also improved after 12 weeks of T-614 therapy. The mean ESR decreased significantly, from 28.1 mm/h to 17.4 mm/h, and the CRP level dropped from 13.0 mg/dL to 4.8 mg/dL ($p < 0.05$) (Figure 1).

T-614 has been widely used for the therapy of RA in Japan and China in recent years. Most studies have focused mainly on the immunosuppressive mechanism of T-614 and its value as an antirheumatic drug, rather than its use as an NSAID. Few studies have paid attention to the anti-

Table 1. Baseline demographic characteristics of axial spondyloarthritis patients.

Parameter	
Gender (male/female)	6/11
Age (years)	49.8 ± 12.8
Age > 45 years	6 (35)
Disease duration (years)	3.52 ± 2.45
Positive HLA-B27	17 (100)
PGA (0–10)	6.91 ± 1.35
ESR (mm/h)	28.1 ± 31.1
CRP (mg/dL)	13.0 ± 11.5
BASDAI	3.57 ± 0.74
ASDAS-CRP	4.85 ± 1.75
Background medications	
NSAIDs	17 (100)
Celebrex	7
Diclofenac	3
Ibuprofen	5
Nimesulide	2
Methotrexate	5 (82)
Leflunomide	1 (27)
Glucosidorum tripterygll totorum	3 (53)
Salazosulfapyridine	10 (24)

Data are shown as n/n, mean ± SD, or n (%).
HLA, human leucocyte antigen; PGA, patient's global assessment of disease activities; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; NSAID, non-steroidal anti-inflammatory drug.

DOI: https://doi.org/10.1080/03009742.2017.1390150

艾拉莫德在伴皮肤损害疾病治疗方案

1、银屑病：艾拉莫德/MTX+艾拉莫德

2、结节性红斑：艾拉莫德/MTX+艾拉莫德

3、皮肤型血管炎：艾拉莫德/MTX+艾拉莫德

4、盘状红斑狼疮：艾拉莫德/羟氯喹+艾拉莫德

5、狼疮皮疹：艾拉莫德和/中小量激素

6、皮肤性血管炎或雷诺现象：可以尝试艾拉莫德和/中小量激素

7、其他类型：联合治疗，艾拉莫德/羟氯喹+糖皮质激素+环磷酰胺

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- ✓ **NSAID样作用：抑制PGE2等**
- ✓ **抗神经痛作用**

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