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UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II
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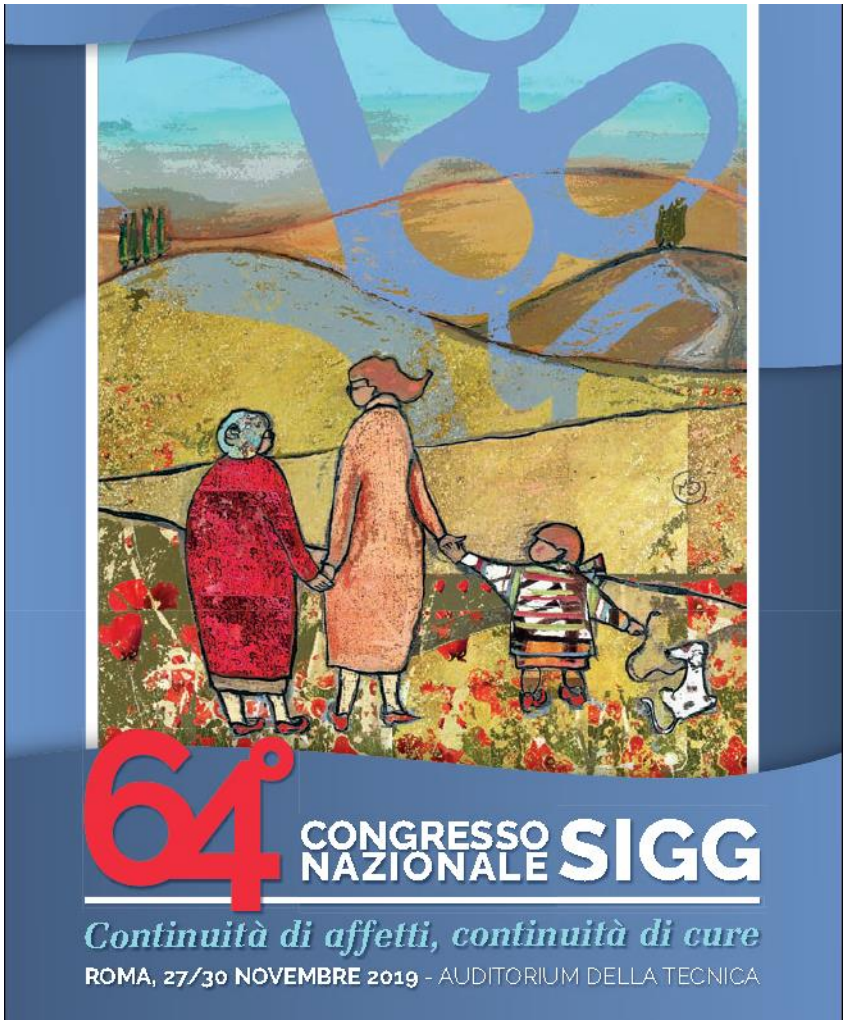

Le Terapie biologiche innovative nel paziente complesso

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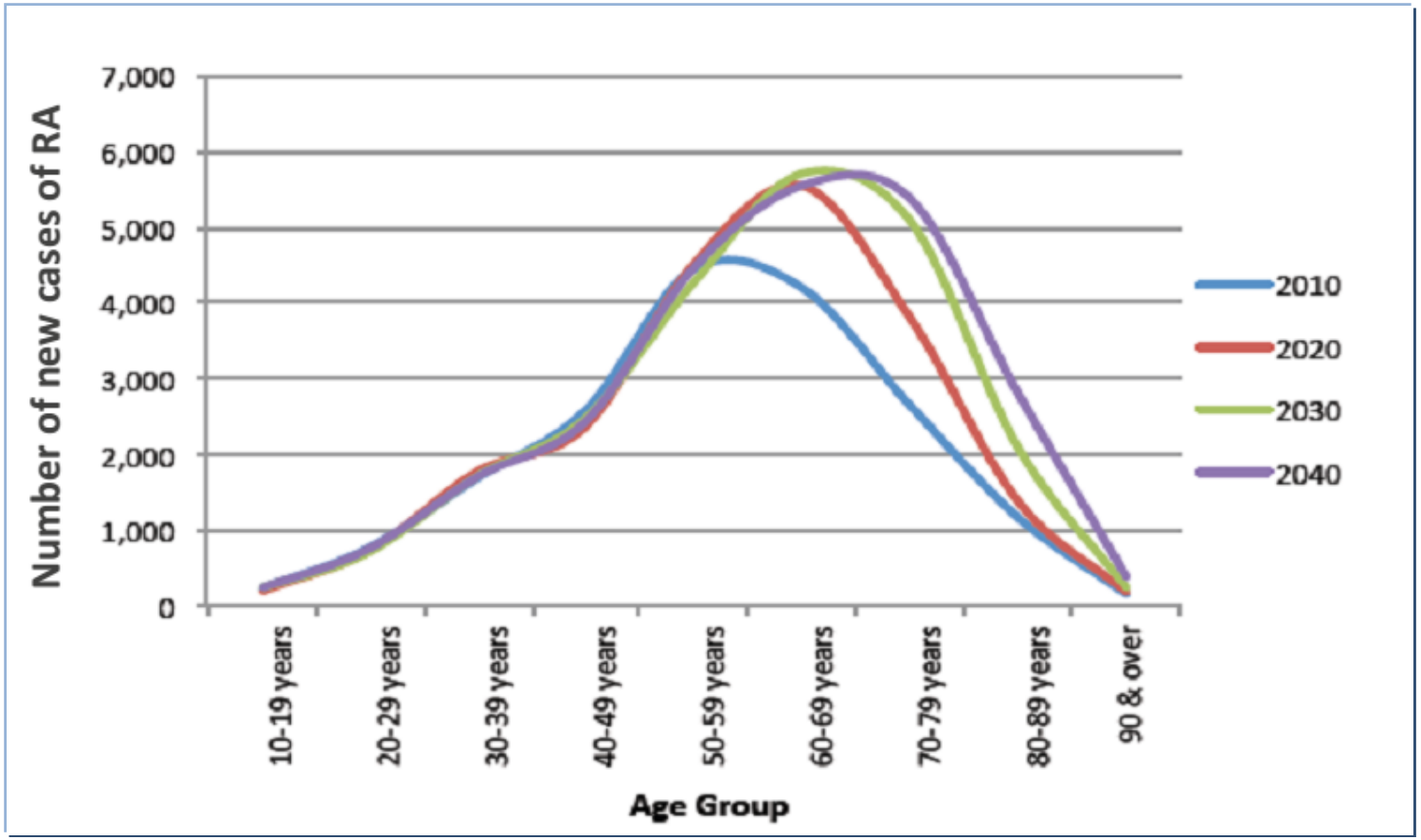
Autoimmune Diseases

- ✓ Almost 5% of the world population develops AD. Of this 5% approximately 80% are women and it is considered the fourth leading cause of disability for them.
- ✓ Considering all diseases in the class, the most common mean age-of-onset was 40–50 years.

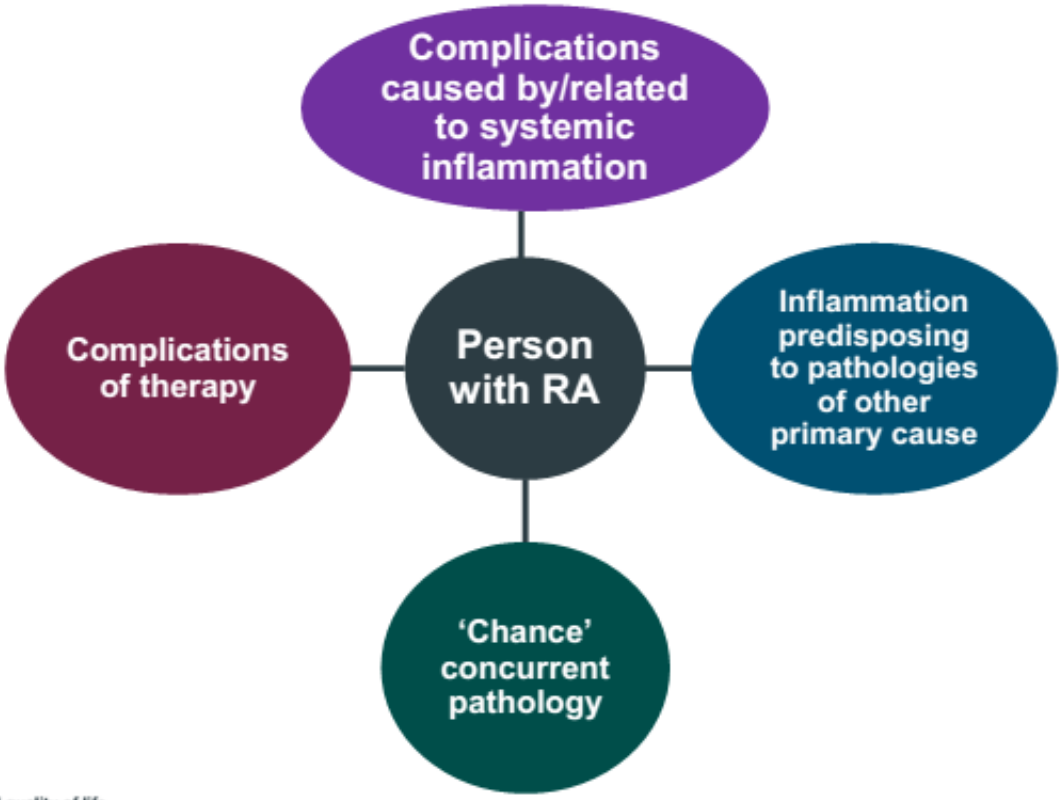
Rheumatoid Arthritis is the Incidence Rising?

The concept of rheumatoid arthritis, a chronic progressive inflammatory disease of the synovial joints, as a disorder of middle age is changing to include patients outside the range of 40 to 60 years.



PLoS One. 2018 Oct 16;13(10):e0205651

A patient-centred concept



Focus of treatment
Patient

Outcome measures
Patient-centred:
HRQoL, disability

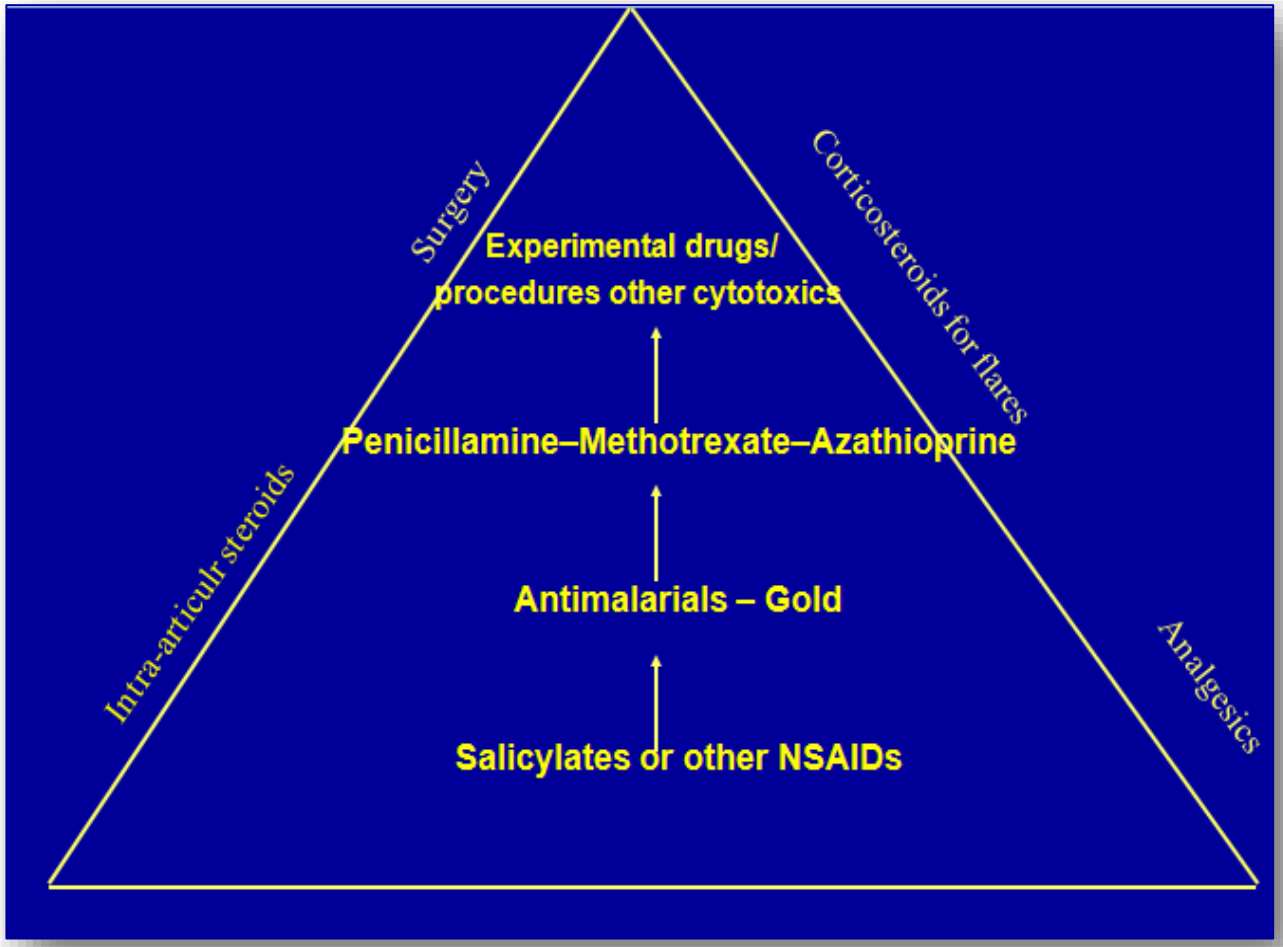
HRQoL, health-related quality of life

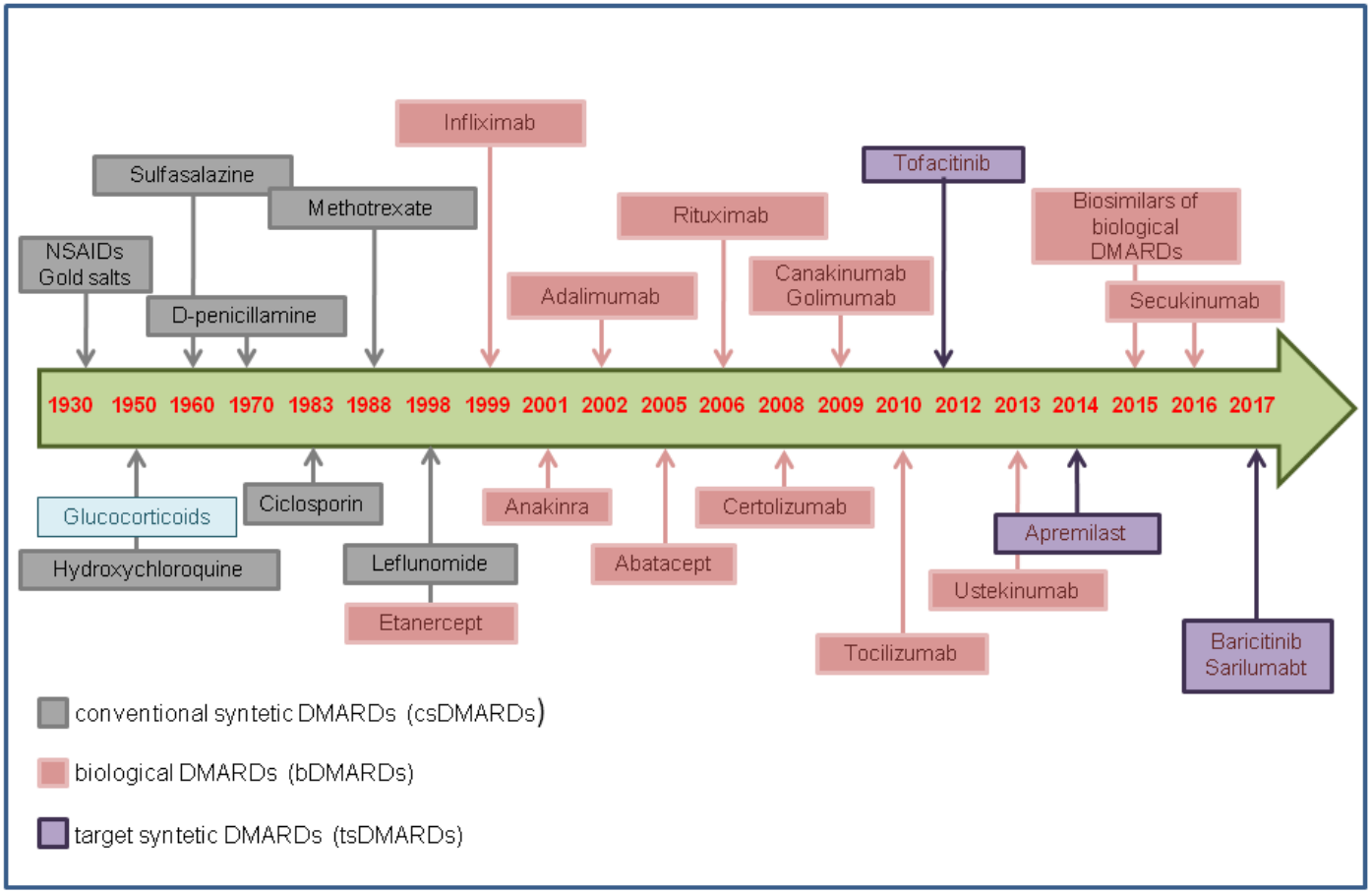
Radner H, et al. *Nat Rev Rheumatol* 2014;10:252–256.

Cause age is one of the major determinants in clinical decision-making, there are distinct considerations for treatment strategies and clinical outcomes for elderly patients with RA.

Traditional Pyramid Model Treatment

The management of rheumatoid arthritis has changed dramatically over the past 30 years. Few therapeutic agents existed then, which were either minimally or not efficacious, because of toxicity and the fact that optimal dosing and onset of action had not yet been elucidated for some agents.





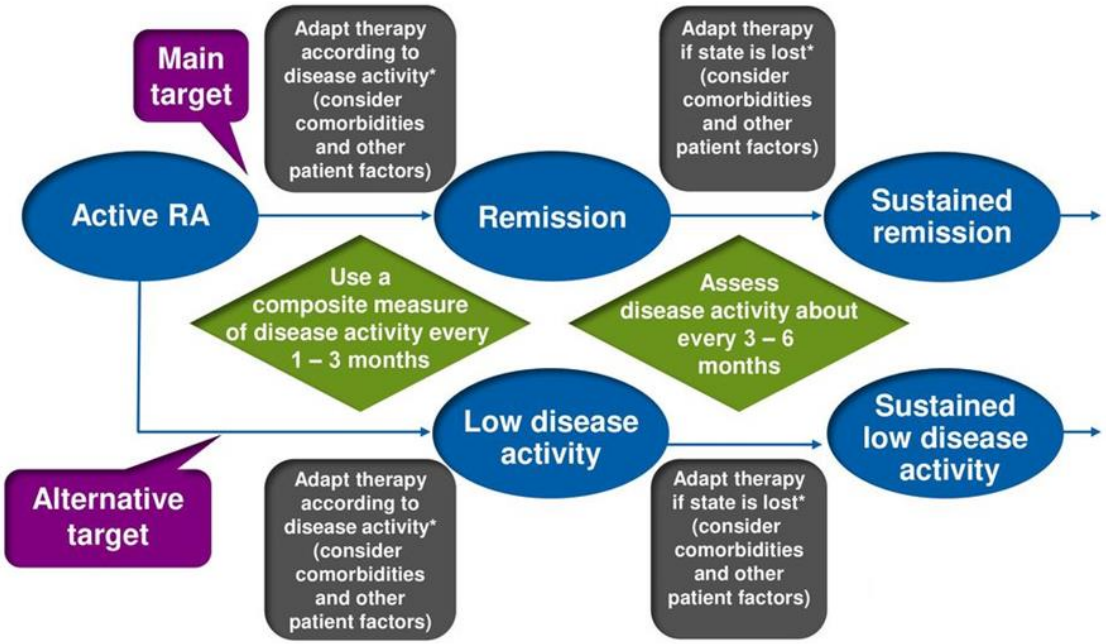
The mechanistic immune classification has implications for understanding the compexity of RA and for thinking about therapy in an **immune-centric way**.

antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		**Biological DMARDs (bDMARDs)**	
Conventional synthetic DMARDs (csDMARDs)	Targeted synthetic DMARDs (tsDMARDs)	Biological originator DMARDs (boDMARDs)	Biosimilar DMARDs (bsDMARDs)

F.W. Rossi et al 2018

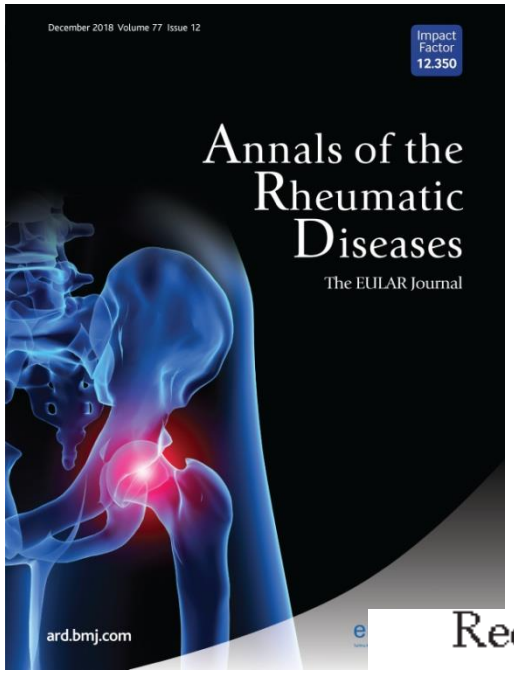
Algorithm for treating rheumatoid arthritis (RA)



These recommendations suggest intensifying the disease-modifying antirheumatic drug (DMARD) strategy, if improvement or the treatment target is not achieved within 3 or 6 months, respectively.

Nevertheless, a significant proportion of patients remains symptomatic after several cycles of treatment, which makes them **difficult to treat (5-20%)**; this is a significant clinical problem in daily practice.

Ann Rheum Dis 2016;75:3-15
Ann Rheum Dis 2017;76:960–977



The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions

The choice of the (composite) measure of disease activity and the target value should be influenced by comorbidities, patient factors and drug-related risks

Recently, a EULAR Task Force has been initiated on the development of recommendations for the comprehensive management of difficult-to-treat RA. The results of this survey will fuel discussions on items to include in the management recommendations of difficult-to-treat RA.

In conclusion, the results of this survey underscore the difficulty in establishing an unambiguous concept of difficult-to-treat RA, which is seen as a heterogeneous condition not fully covered by current EULAR recommendations. The recently established EULAR Task Force will explore the management of difficult-to-treat RA further.

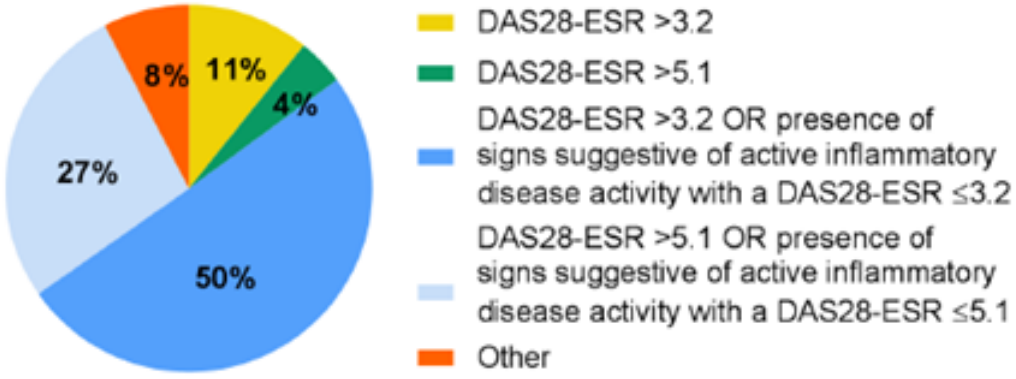
Ann Rheum Dis 2018;77:120

Difficult-to-treat RA

1. There is no definition of difficult to treat RA.
2. Difficult to treat RA is a multifactorial condition in which, for each individual patient, different factors may be major determinants of persistence of sign and sympthoms, which is seldom caused by drug resistance only.
3. The poor understanding of characteristics, mechanisms and biological correlates of these factors hamper clinical decision making.
4. Multiple different factors can lead to drug discontinuation or difficulty in grading RA activity.
5. The complex interplay of contributory factors indicates an individualized management approach for difficult-to-treat RA patients.

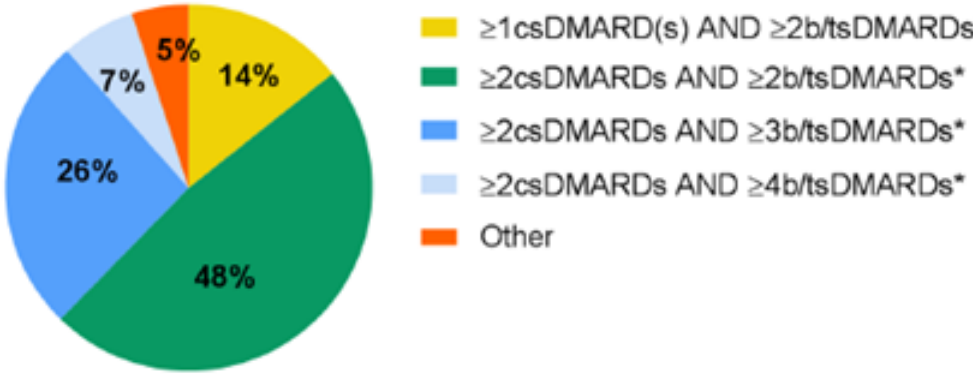
Rheumatology 2018;57:11351144

A. What should be the definition for not well-controlled disease in the definition of difficult-to-treat RA?



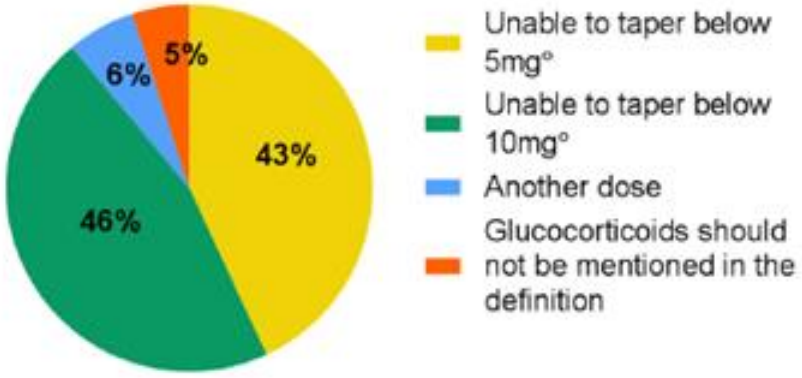
Total responses = 409

C. Which and how many antirheumatic drugs should at least be tried with insufficient effect for the definition of difficult-to-treat RA?



Total responses = 398

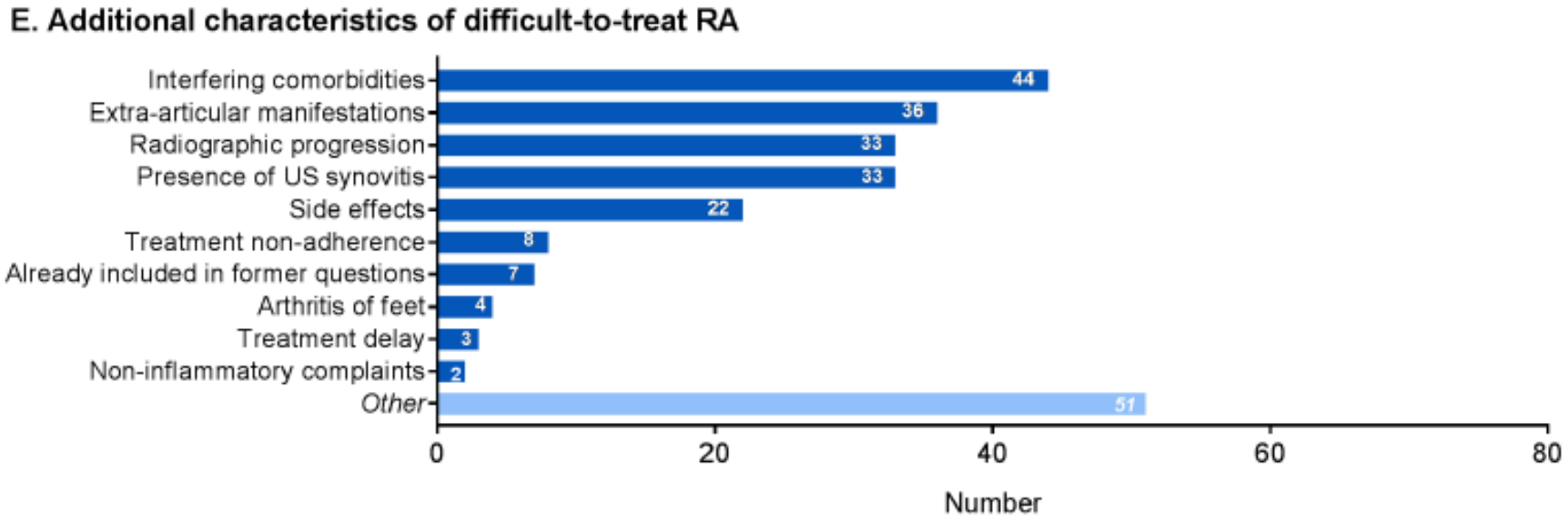
D. Treatment with glucocorticoids should be mentioned in the criteria for difficult-to-treat RA as follows:



Total responses = 397

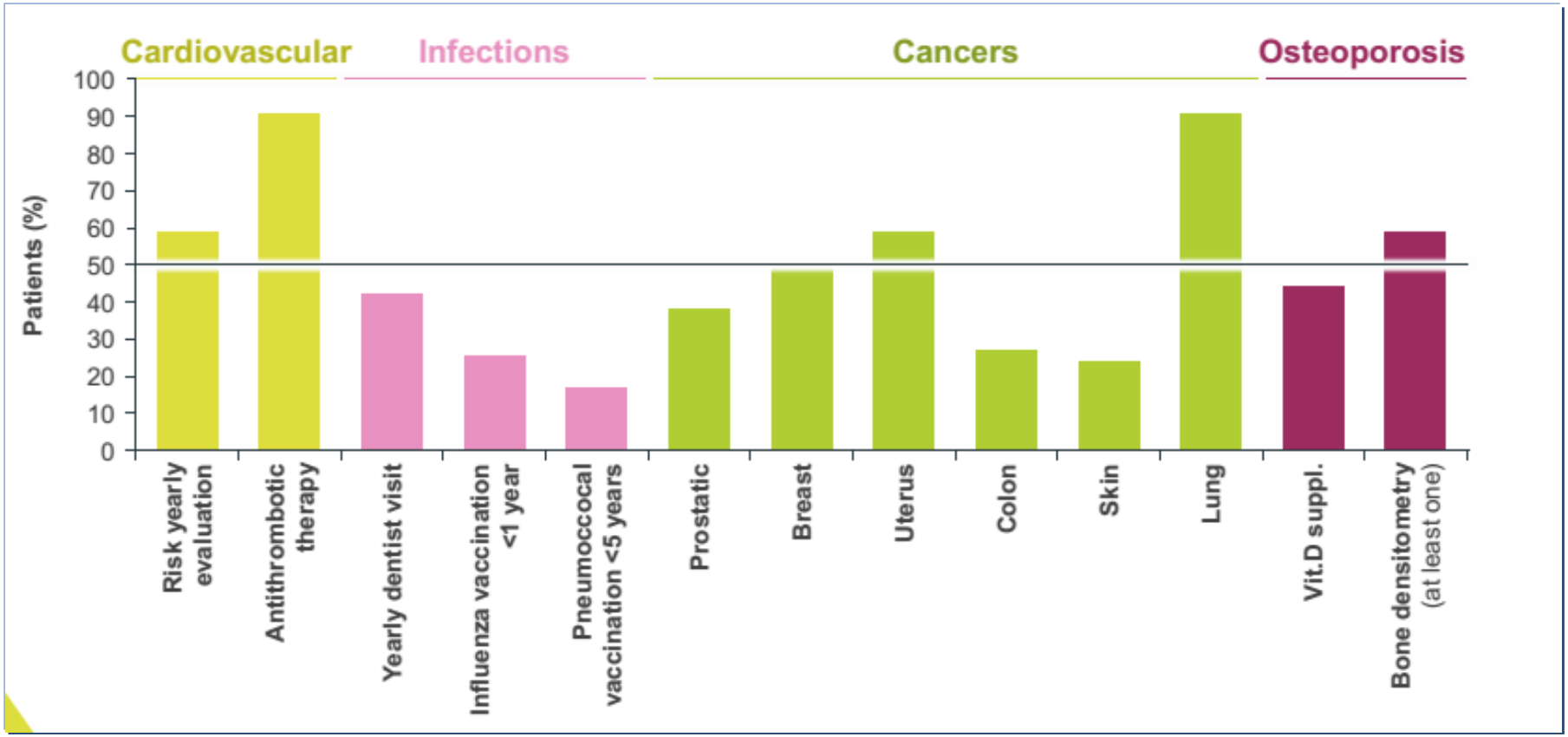
Ann Rheum Dis 2018;77:120

Difficult-to-treat RA



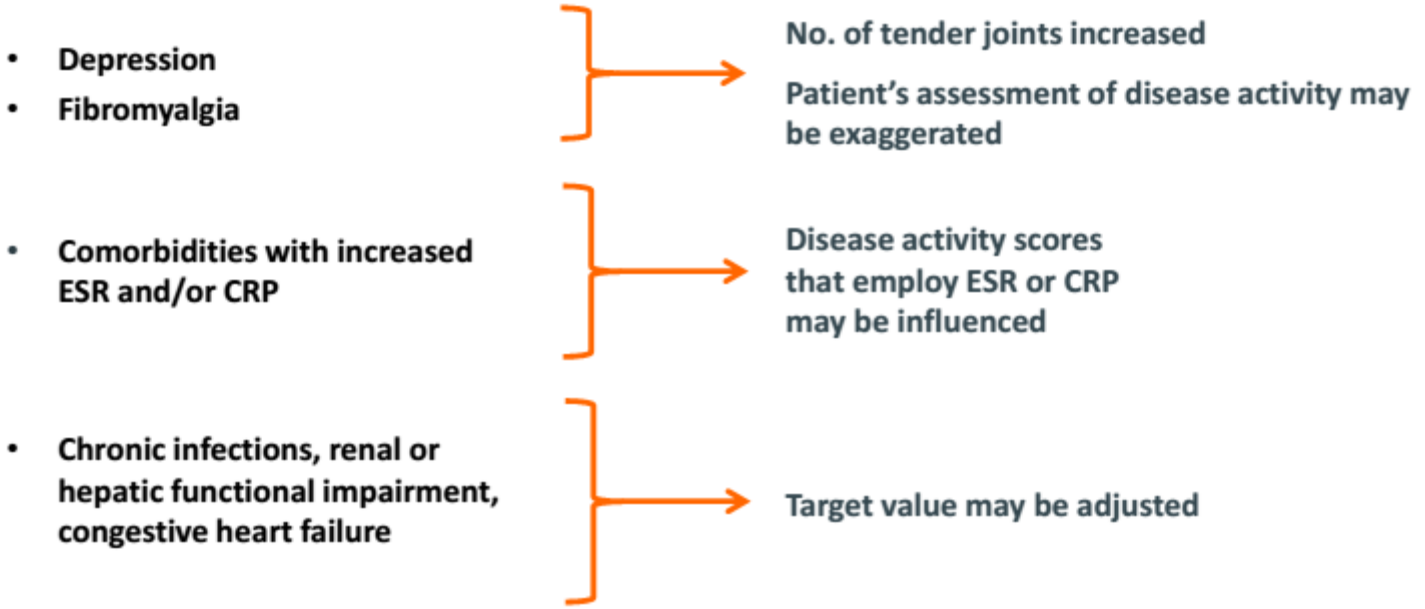
Ann Rheum Dis 2018;77:120

How do we deal with RA-related comorbidities? The COMORA study



Ann Rheum Dis 2014;73:62

Considerations of comorbidities and disease activity measures

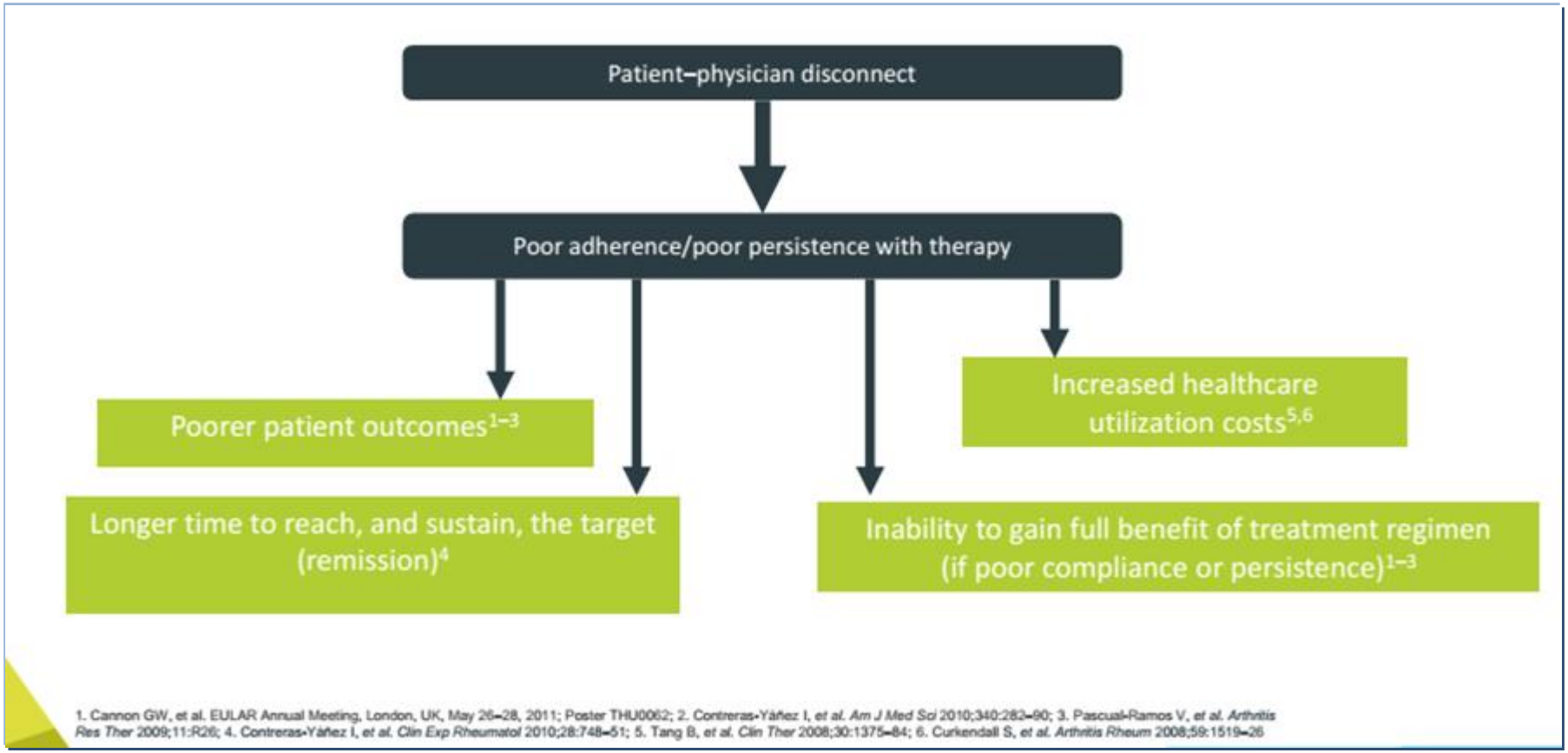


ESR, erythrocyte sedimentation rate

Smolen JS, et al. *Ann Rheum Dis* 2010;69:631–7

Ann Rheum Dis 2014;73:62

Patient-Physician disconnect: a chain of problematic events ensues



1. Cannon GW, et al. EULAR Annual Meeting, London, UK, May 26–28, 2011; Poster THU0062; 2. Contreras-Yáñez I, *et al. Am J Med Sci* 2010;340:282–90; 3. Pascual-Ramos V, *et al. Arthritis Res Ther* 2009;11:R26; 4. Contreras-Yáñez I, *et al. Clin Exp Rheumatol* 2010;28:748–51; 5. Tang B, *et al. Clin Ther* 2008;30:1375–84; 6. Curkendall S, *et al. Arthritis Rheum* 2008;59:1519–26

Systemic or extra-articular manifestations

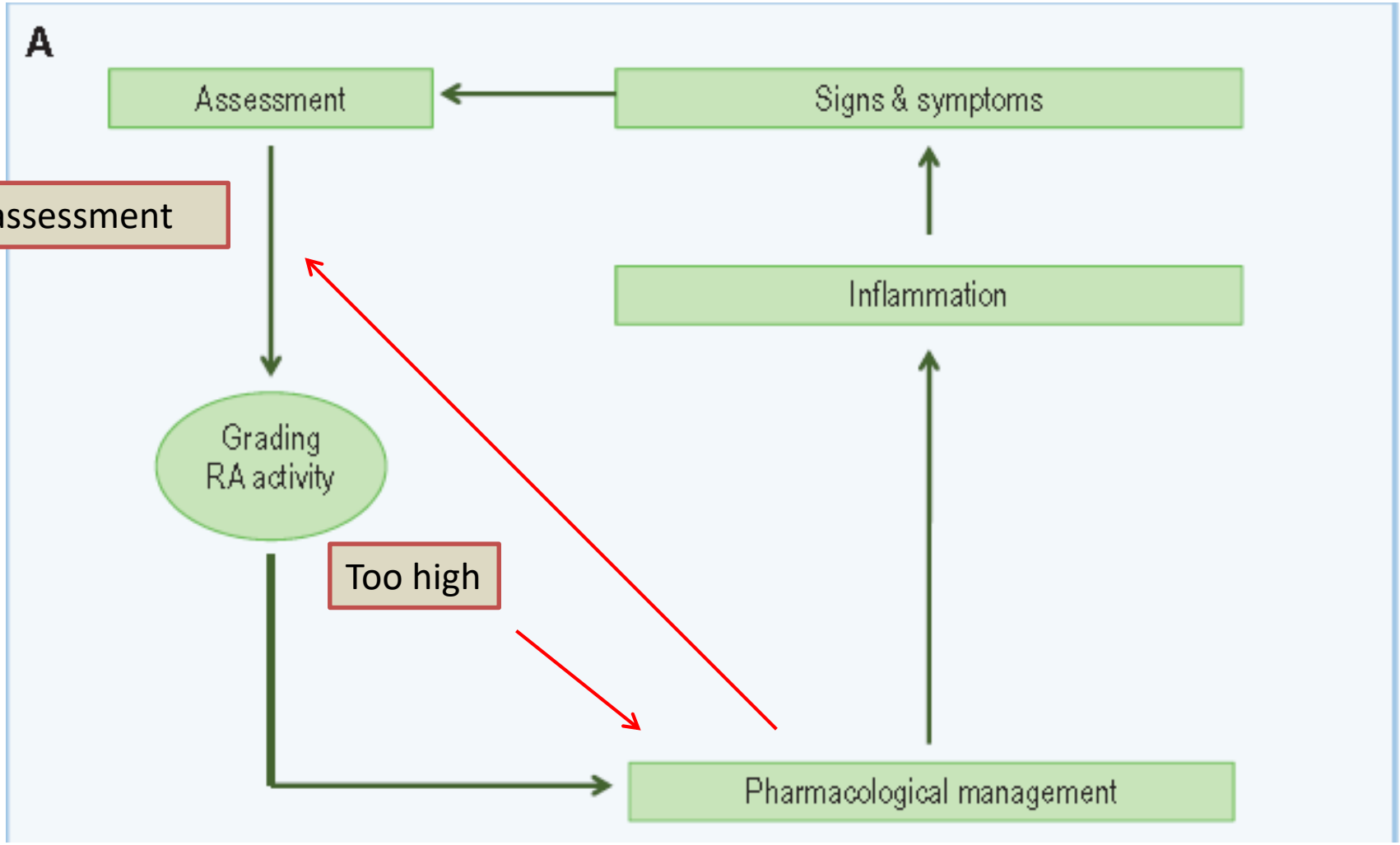
- Systemic or extra-articular manifestations are common in patients with rheumatoid arthritis (RA).

- The prevalence of systemic manifestations reported in studies of RA is approximately 8% up to 40%.

- Extra-articular manifestations of RA are associated with significant morbidity and increased mortality.

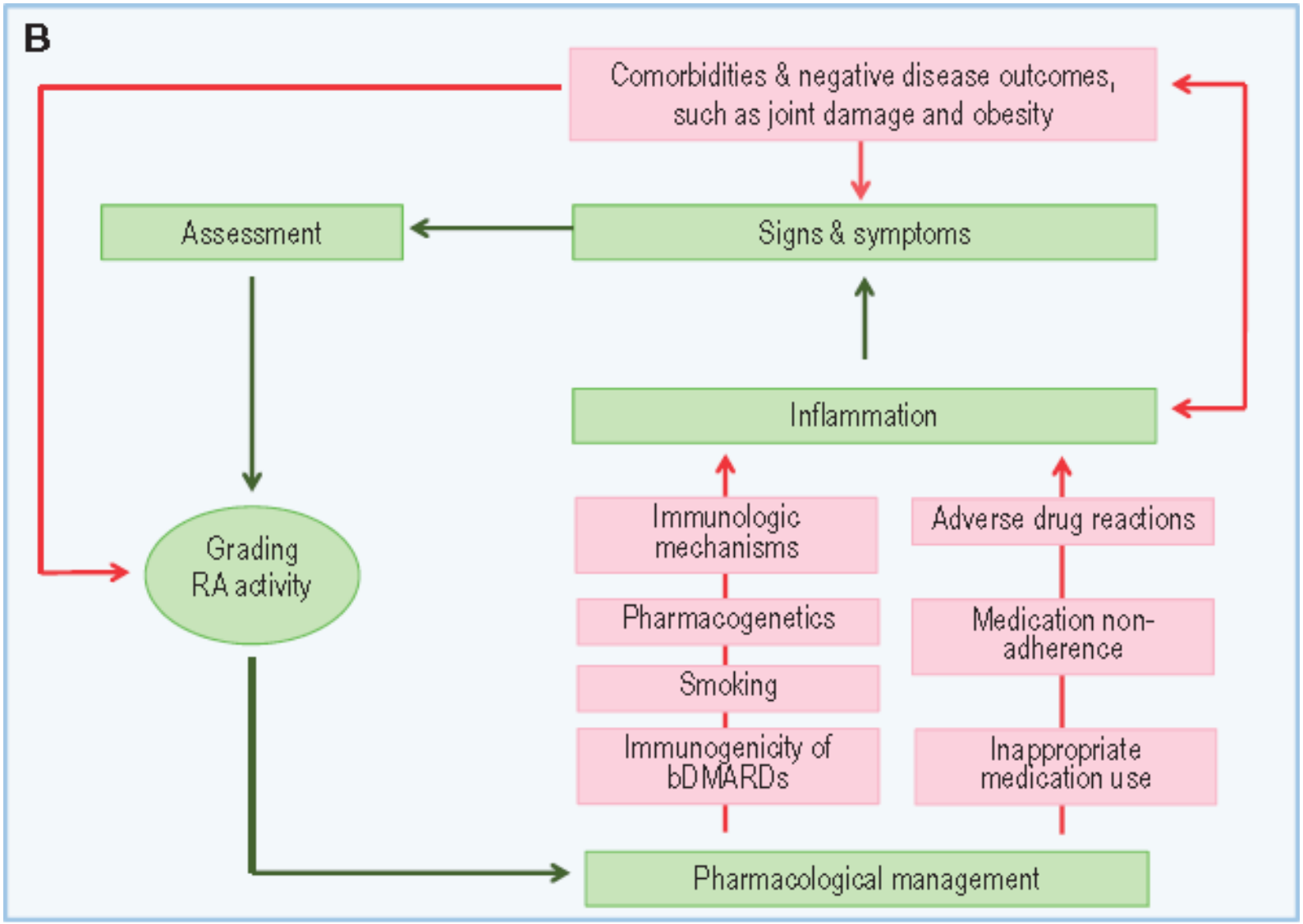
- Many of the extra-articular manifestations of RA are associated with increased disease activity and with markers of inflammation.

The management cycle of uncomplicated RA



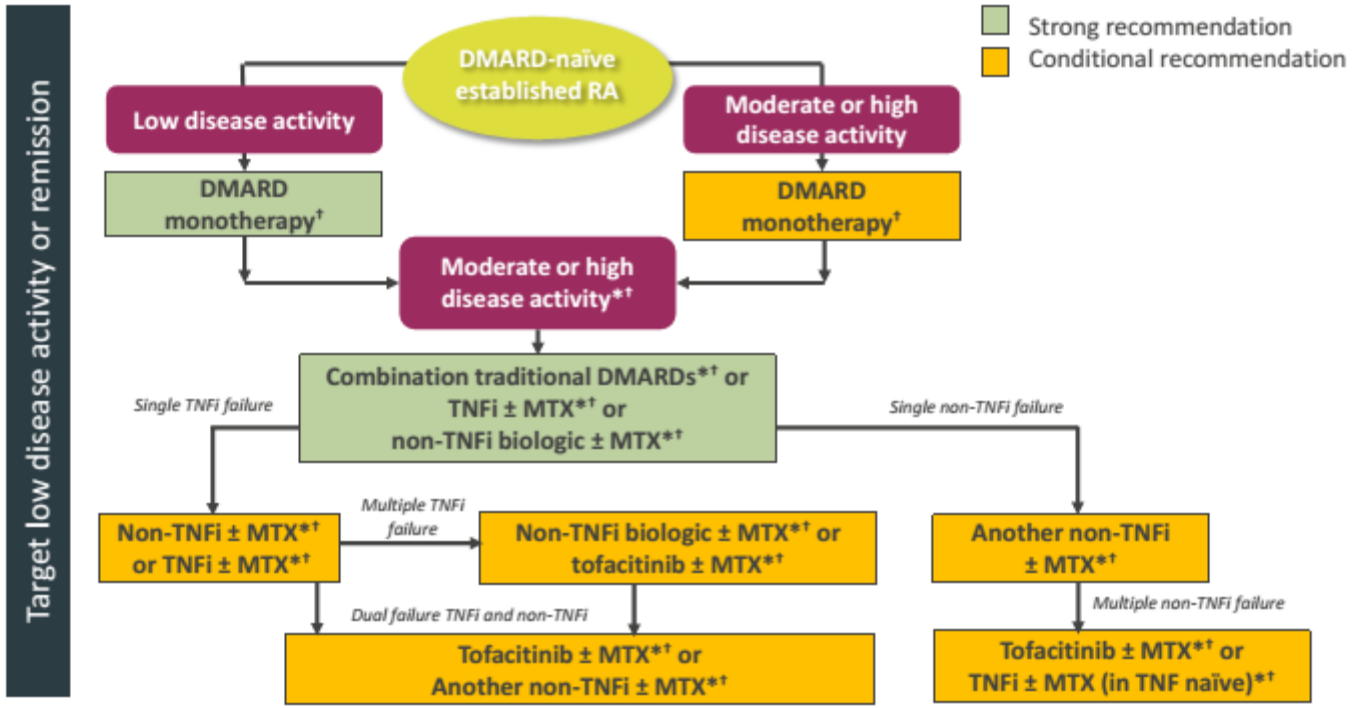
Reumatology 2018; 57:1135-1144

The management cycle of complicated / difficult-to-treat RA



Reumatology 2018; 57:1135-1144

ACR 2015 guidelines: established RA (≥6 months)



*Consider adding low-dose glucocorticoids (<10 mg/day of prednisone or equivalent); †Consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares

Singh J, *et al. Arthritis Care Res* 2016;68:1–25

Special situations: congestive heart failure

- In patients with established RA **with moderate or high disease activity and NYHA class III or IV CHF**, we conditionally recommend using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNFi

- If patients in this population are **treated with a TNFi and their CHF worsens while on the TNFi**, we conditionally recommend switching to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNFi

CHF, congestive heart failure; NYHA, New York Heart Association

Singh J, *et al. Arthritis Care Res* 2016;68:1–25

Special situations: hepatitis B

- In patients with established RA with **moderate or high disease activity and evidence of active hepatitis B** infection (hepatitis surface antigen positive >6 months), **who are receiving or have received effective antiviral treatment**, we strongly recommend treating them the same as patients without this condition
- For a patient with natural **immunity from prior exposure to hepatitis B** (i.e., HB core antibody and HBS positive and normal liver function tests), we recommend the same therapies as those without such findings as long as the patient's viral load is monitored
- For patients with **chronic hepatitis B who are untreated**, referral for antiviral therapy is appropriate prior to immunosuppressive therapy

HB, hepatitis B; HBS, hepatitis B surface antibody

Singh J, *et al. Arthritis Care Res* 2016;68:1–25

Special situations: hepatitis C

- In patients with established RA with **moderate or high disease activity and evidence of chronic** HCV infection, **who are receiving or have received effective antiviral treatment**, we conditionally recommend treating them the same as the patients without this condition
- We recommend that rheumatologists work with gastroenterologists and/or hepatologists who would monitor patients and reassess the appropriateness of antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which may lead to a greater number of HCV patients being treated successfully.
- If the same **patient is not requiring or receiving antiviral treatment for their hepatitis C**, we conditionally recommend using DMARD therapy rather than TNFi

HCV, hepatitis C virus

Singh J, *et al. Arthritis Care Res* 2016;68:1–25

Special situations: malignancies

Previous melanoma and non-melanoma skin cancer

- In patients with established RA and moderate or high disease activity and a **history of previously treated or untreated skin cancer** (melanoma or non-melanoma), we conditionally recommend the use of DMARD therapy over biologics or tofacitinib

Previous lymphoproliferative disorders

- In patients with established RA with moderate or high disease activity and a **history of a previously treated lymphoproliferative disorder**, we strongly recommend using rituximab rather than a TNFi and conditionally recommend using combination DMARD therapy, abatacept or tocilizumab rather than TNFi

Previous solid organ cancer

- In patients with established RA with moderate or high disease activity and **previously treated solid organ cancer**, we conditionally recommend that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer

Singh J, *et al. Arthritis Care Res* 2016;68:1–25

Special situations: serious infections

- In patients with established RA with moderate or high disease activity and **previous serious infection(s)**, we conditionally recommend using combination DMARD therapy or abatacept rather than TNFi

RHEUMATOLOGY

Rheumatology 2019;58:1367–1377
doi:10.1093/rheumatology/key433
Advance Access publication 21 January 2019

Original article

Comparative effectiveness of abatacept, rituximab, tocilizumab and TNFi biologics in RA: results from the nationwide Swedish register

Thomas Frisell[1], Mats Dehlin[2], Daniela Di Giuseppe [1], Nils Feltelius[3], Carl Turesson[4,5] and Johan Askling[1] on behalf of the ARTIS Study Group*

Current guidelines rank abatacept, rituximab, tocilizumab and TNF-inhibitors (TNFi) as having equal effectiveness for the treatment of RA, at least as second line therapies.

Treatment outcomes among RA patients treated in Swedish clinical practice are in line with a superior effectiveness of non-TNFi bDMARDs, in particular tocilizumab and rituximab, compared with TNFi.

Conclusions

✓Current management recommendations (treat-to-target / EULAR / ACR) do not cover management of comorbid conditions;

✓Treat-to-target recommendations make a strong case on considering comorbidities when choosing the target scale and setting the numerical target;

✓The ACR guidelines consider various comorbidities and their implications for therapy of RA;

✓Age is one of the major determinants in clinical decision-making;

✓Due to the lack of knowlendge about the different weight of contributing factors of difficult-to treat RA in clinical practice treatment steps and decision for each patient are based on trial and error;

✓Until an effective treatment regimen or approach is found, patients continue to suffer from sign and sympthoms that impact directly their social life, work ability and quality of life;

✓Beside the personal impact, difficult to treat RA also affect negatively health care utilization, hospital budgets and society cost.

Reumatology 2018; 57:1135-1144

The World Incidence and Prevalence of Autoimmune Diseases is Increasing

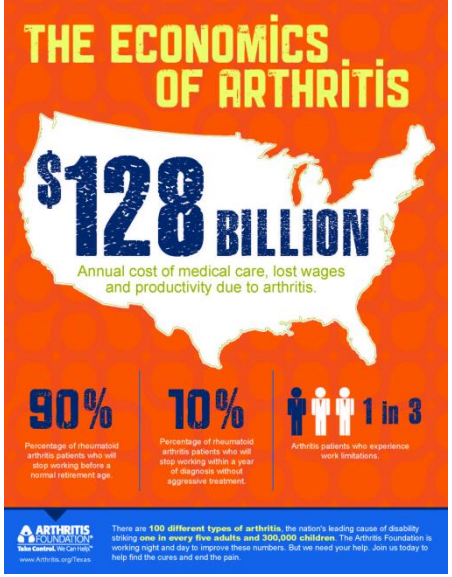
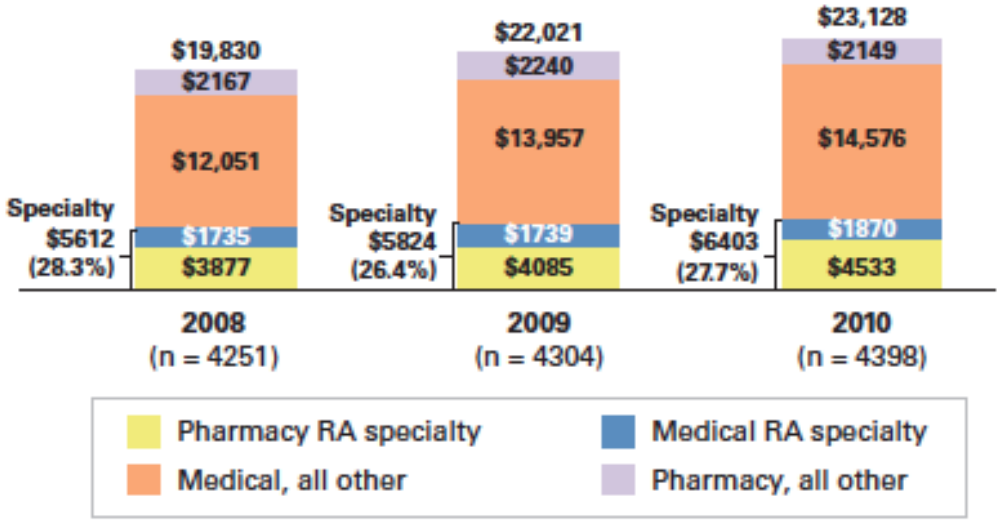


Figure. Annual Average Cost of Care for Rheumatoid Arthritis Patients[9]



RA indicates rheumatoid arthritis.
Reprinted with permission from Gleason PP, et al. *J Manag Care Pharm*. 2013;19:542-548.