Remission in RA

"The primary target for treatment of RA should be a state of clinical remission."

Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Smolen et al

Higher remission rates are achieved when treating patients with early disease

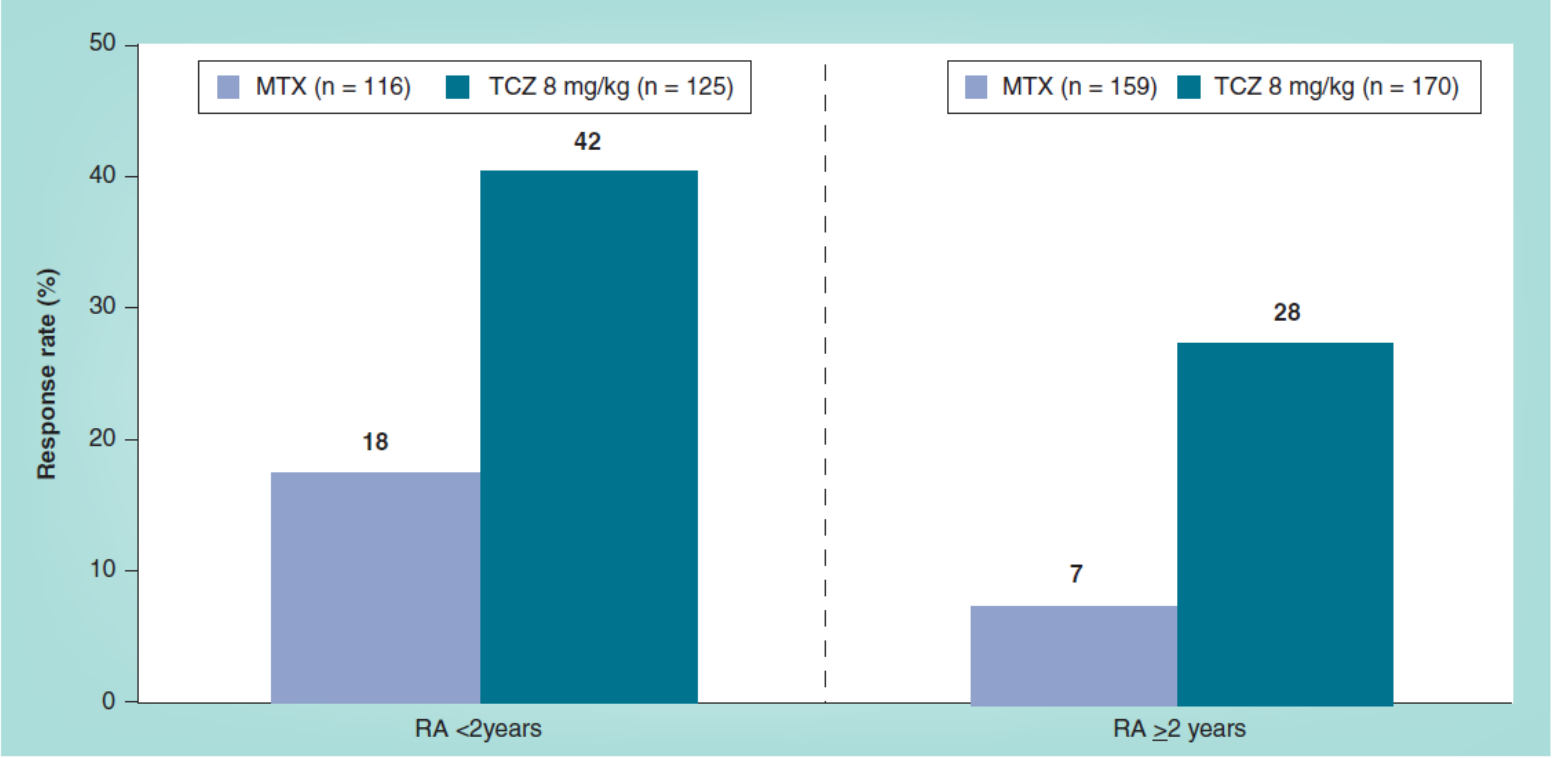


Figure 5. Clinical remission (disease activity score 28 <2.6) at week 24 is higher in patients with rheumatoid arthritis <2 years (intent to treat).

MTX: Methotrexate; RA: Rheumatoid arthritis; TCZ: Tocilizumab.

Timeline of RA

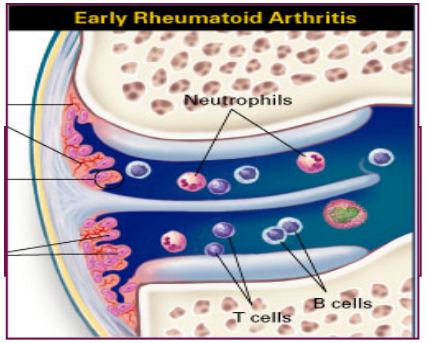
Opportunities for achieving higher remission

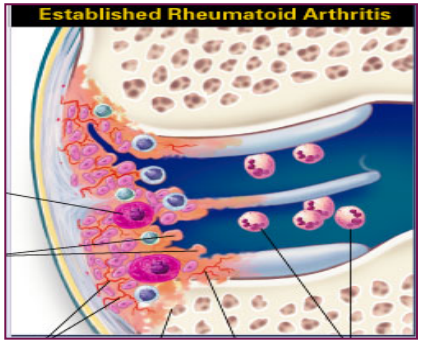
- Increased synovial tissue mass
- Progressive joint destruction
- Epigenetic changes

Autoantibodies

Arthritis

Initiation of synovial inflammation





Early RA *Long-standing RA*

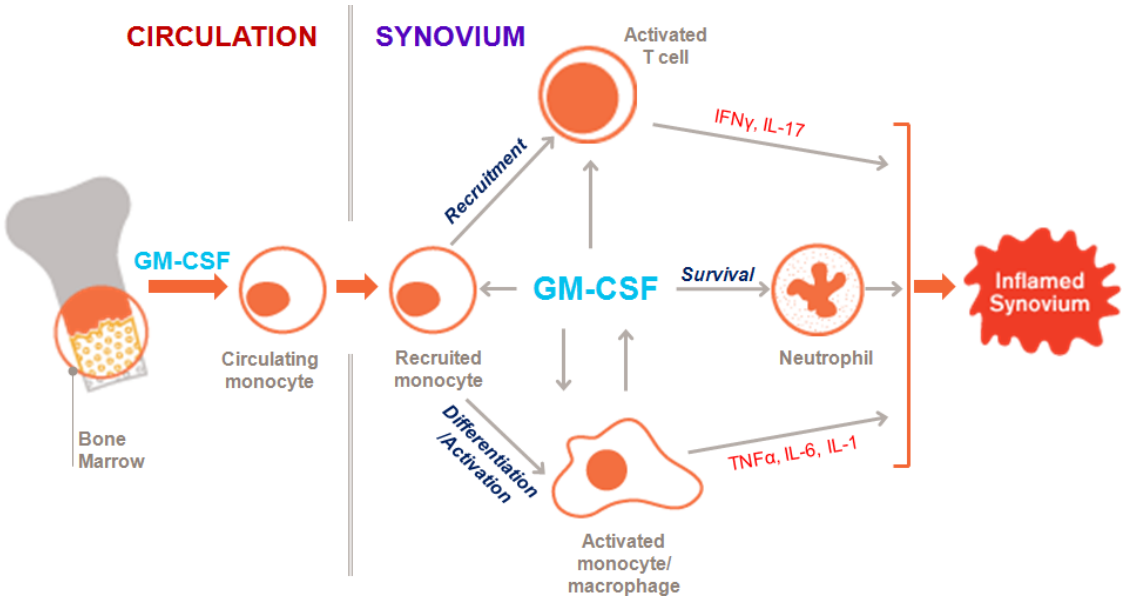
Therapeutic "window of opportunity"

Tak, PP. Best Pract Res Clin Rheumatol 2001; 15:17–26M and vd Sande et al. Ann Rheum Dis. 2011;70:772-7

Clinical improvement in RA is consistently associated with decreased macrophage infiltration

GM-CSF plays a key role in activation of macrophages at the site of injury or inflammation

- Activated macrophages are abundantly expressed in early RA synovial tissue, representing the predominant cell type
- Macrophage is a primary cause of tissue destruction and affects many other cell types
- Reduction in macrophage infiltration correlates with improvement in disease activity scores[1,2]
- GM-CSF plays a key role in macrophage production and infiltration in the tissues
- By blocking GM-CSF, GSK3196165 will interfere with this key effector cell more effectively than by blocking the effects of TNFa or IL-6 alone.
- Macrophage related biomarkers (e.g. MRP8/14, CXCL-13) might allow identification of responders able to achieve remission, facilitating a precision medicine approach.



[1] Boumans MJ, Thurlings RM, Gerlag DM, Vos K, Tak PP. Arthritis Rheum. 2011;63:3187-94.
[2] Bresnihan B, Pontifex E, Thurlings RM, et al. J Rheumatol 2009;36:1800-2.

Anti-GM-CSF and RA: Development Challenges

Targeting a New Paradigm in an Established Setting

	Traditional Approach	New Paradigm
Population	DMARD-IR/Biologic-IR	Early disease “window of opportunity”
Endpoint	Reduction in disease activity (ACR20/50)	Definition of biologic-free remission
Control	Placebo or active comparator (parallel group)	Requires randomised-withdrawal (own control)
Treatment approach	Chronic generally at full dose if reduction (even modest) is achieved	-Induction of sustained remission followed by withdrawal of biologic in responders -Early identification of responders/non-responders
Follow-up	Open label extension (on treatment)	Demonstration of maintenance of biologic-free remission