Impact of Drug Induced Remission in Rheumatoid Arthritis

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LUND
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Objectives:

The overall aim of the thesis is to examine different aspects of remission in patients with rheumatoid arthritis (RA) with a particular focus on sustained remission (SR). Specifically, the objectives were to study (i) the frequency, possible baseline predictors, timing and duration of SR (ii) the difference between anti-TNF medications used as first biological treatment with regard to frequency, duration and timing of SR (iii) the possible beneficial effect of SR compared to occasionally reaching remission with respect to physical function measured by HAQ (iv) different types of remission criteria and their possible effect on SR and (v) secular trends in remission and SR in RA.

Methods:

Data from all adult patients with RA included in a regional rheumatology register (The South Swedish Arthritis Treatment Group register; SSATG) and the national quality register (The Swedish Rheumatology Quality register; SRQ) were analysed. Patients fulfilling different remission criteria and patients in SR, defined as remission for at least 6 months and during at least two consecutive visits, were identified. Fulfilling remission criteria occasionally but not SR was defined as non-sustained remission (NSR). Patients in SRQ were categorized as early RA (<6 months from symptom onset to inclusion in the registry) or established RA.

Results:

In the national SRQ registry, approximately 70% of patients reached remission at any time point (DAS28<2.6) and 41.9% fulfilled the critera for SR. SR was more common in early RA ($p<0.001$). In SSATG, only 15.8% of patients with established RA who were treated with anti-TNF drugs reached SR. Most patients escaped after the first visit in remission but once in SR patients stay in SR for considerable time. Median time in SR was 7.2 (SRQ) and 5.3 (SSATG) years and many patients were still in remission at the last follow up. Median time from symptom onset to SR was 1.9 (SRQ) and from anti-TNF start to SR 0.7 (SSATG) years.

Lower age, male sex, early RA and lower disease activity were associated with SR in SRQ. Positive predictors of SR in anti-TNF treated patients were: male sex, low HAQ, low DAS28, methotrexate treatment, and the calendar year of treatment start.

Comparing the SR and NSR groups, HAQ improved during the first 12 months and continued to improve as long as DAS28 SR was maintained. A higher proportion of patients in SR reached full physical function.

Before year 1992 remission was extremy uncommon among patients with RA. Thereafter the proportion of patients reaching SR increased significanly every other year until 2009. Among patients with disease onset in 2009, five years after symptom onset 45.3% of patients had reached SR. Corresponding figures for 1990 and 1999 were 0% and 15.9%, respectively.

Conclusions:

A considerable proportion of patients with RA in Sweden never reach SR. However, once in SR patients remain in SR for a substantial period of time. Patients with early RA are more likely to reach SR than patients with established RA. In patients with established RA, physical function improves in patients reaching SR compared with patients reaching remission occasionally. Maintaining SR should be a treatment goal.

There is a clear secular trend towards increased incidence of sustained remission in patients with RA in Sweden. This trend most likely reflects earlier diagnosis and treatment start and adherence to national and international guidelines recommending the 'treat to target' approach.

Key words: Rheumatoid Arthritis, Sustained Remission, Outcome measures, Anti-TNF , Secular trends, HAQ

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Coverphoto by Bertha Ágústa Einarsdóttir (my sister). Geysir í Haukadal.

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Content

Abbreviations

ACR	American College of Rheumatology
ACPA	antibodies to citrullinated protein antigen
ADA	Adalimumab
bDMARD	biological disease-modifying antirheumatic drug
CI	confidence interval
CRP	c-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CVD	cardiovascular disease
CZP	Certolizumab-pegol
DAI	disease activity index
DAS	disease activity score using 44-joint counts
DAS28	disease activity score using 28-joint counts
DMARDs	disease-modifying antirheumatic drugs
EGA	evaluator global assessment of disease activity
ESR	erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League against Rheumatism
EQ-5D	European Quality of Life-5 Dimensions
GH	global health
GC	glucocorticoids
HAQ	health assessment questionnaire
HAQ-DI	health assessment questionnaire disability index
HR	hazard ratio
IFX	Infliximab
LDA	low disease activity
LUNDEX	LUND Efficacy index
MCP	metacarpophalangeal
MTP	metatarsophalangeal
MTX	methotrexate
MHAQ	modified health assessment questionnaire
NSR	non-sustained remission
PIP	proximal interphalangeal
PROs	patient reported outcomes
PtGA	patient global assessment of disease activity
RA	rheumatoid arthritis
RF	rheumatoid factor
RR	relative risk
SDAI	Simplified Disease Activity Index
SJC	swollen joint count including 28 joints
SR	sustained remission

SRQ	Swedish National Rheumatology Quality Registry
SSATG	South Swedish Arthritis Treatment Group
TJC	tender joint count including 28 joints
TNF	tumour necrosis factor
UA	undifferentiated arthritis
UK	United Kingdom
VAS	visual analogue scale

Introduction

This thesis deals with the concept of remission in rheumatoid arthritis, with special focus on remission that is sustained over time. Our hypothesis has been that sustained remission has benefits that surpass the benefits of reaching remission occasionally and that sustained remission should be the goal of treatment, at least in early disease. The thesis investigates:

- The frequency, prevalence and timing of sustained remission
- Possible predictors of sustained remission
- Possible benefits of sustained remission
- Secular trends in remission and sustained remission

List of papers

This thesis is based on the following papers, which will be referred to by their Roman numerals in the text.

I. **Einarsson, Jon Thorkell**, Pierre Geborek, Tore Saxne, and Meliha C. Kapetanovic. Sustained Remission in Tumor Necrosis Factor Inhibitor–treated Patients with Rheumatoid Arthritis: A Population-Based Cohort Study. *The Journal of Rheumatology* 2016:**42** (5): 741–748.

II. **Einarsson, Jon Thorkell**, Pierre Geborek, Tore Saxne, Lars Erik Kristensen, and Meliha C. Kapetanovic. Sustained Remission Improves Physical Function in Patients with Established Rheumatoid Arthritis, and Should Be a Treatment Goal: A Prospective Observational Cohort Study from Southern Sweden. *The Journal of Rheumatology* 2016:**43** (6):1017–1023.

III. **Einarsson, Jon Thorkell**, Minna Willim, Tore Saxne, Pierre Geborek, Sofia Ernestam, and Meliha C. Kapetanovic. Prevalence of Sustained Remission in Patients with Rheumatoid Arthritis in Sweden. Impact of Criteria Sets and Early Treatment, a Nationwide Study in Sweden. 2017. *Submitted manuscript under revision.*

IV. **Einarsson, Jon Thorkell**, Minna Willim, Tore Saxne, Pierre Geborek, Sofia Ernestam, and Meliha C. Kapetanovic. Secular trends of Sustained Remission in Patients with Rheumatoid Arthritis in Sweden, a Nationwide Study in Sweden. 2017. *Manuscript*.

Some additional observations not previously presented have been included in the results section of this thesis. The articles are reprinted with permission from the publishers.

Related paper not included in the thesis

I. **Einarsson, Jon Thorkell**, Max Evert, Pierre Geborek, Tore Saxne, Maria Lundgren, and Meliha C. Kapetanovic. Rituximab in Clinical Practice: Dosage, Drug Adherence, Ig Levels, Infections, and Drug Antibodies. Clinical Rheumatology, *Clinical Rheumatology* **36** (12) (2017): 2743–50.

Populärvetenskaplig sammanfattning

Reumatoid artrit

Reumatoid artrit (RA, ledgångsreumatism) är en kronisk autoimmun sjukdom. I Sverige är prevalensen bland vuxna runt 0.75%. Man kan insjukna i alla åldrar. RA är 2-3 gånger vanligare hos kvinnor. Orsaken till sjukdomen är inte klarlagd, men olika genetiska och miljöfaktorer i kombination påverkar risken att insjukna. Ett antal faktorer relaterade till levnadsvanor, t.ex. rökning, har en stor inverkan, inte bara på uppkomsten utan även på förlopp och effekt av farmaka.

RA engagerar framförallt leder och senskidor och ger upphov till värk, stelhet och svullnad. Dessutom lider många patienter av trötthet och allmänt illabefinnande. Naturalförloppet vid RA är mycket varierande hos olika patienter och är svårt att förutsäga hos den enskilde patienten. Obehandlad leder RA till funktionsinskränkning med nedsatt arbetsförmåga och ökad risk för hjärtkärlsjukdomar. De senaste 20-30 åren har behandlingen förbättrats dramatiskt vilket har lett till att många patienter som insjuknar i dag kan ha ett aktivt liv.

Den största förändringen av behandlingen innebär tidig och konsekvent hämning av den inflammation som alltid föreligger. Tre huvudprinciper vägleder modern behandling: 1) tidig diagnos 2) snabb utvärdering av effekten av insatt behandling (tight-control) 3) målet för behandlingen är att helt eliminera sjukdomsaktivitet och inflammation (treat-to-target). Målet kan dock variera mellan olika patienter och det är viktigt att ta hänsyn till den enskilde patientens situation.

Utveckling av olika instrument för att skatta sjukdomsaktivitet och funktionsförmåga som stöd för utvärdering av behandling har varit en förutsättning för behandlingsframgångarna. För sjukdomsaktivitet har det visat sig bäst att använda kombinerade aktivitetsindex som väger in graden av inflammation och tar hänsyn till patientens upplevelser av sjukdomen. Ett sådant är DAS28, som väger in antalet svullna och ömma leder, graden av inflammation (mätt med sänkan) samt patientens egen bedömning av sitt generella hälsotillstånd. Funktionsförmåga skattas oftast med en patientenkät med 20 olika frågor kring vardagliga aktiviteter (HAQ, health assessment questionnaire). HAQ är ett viktigt mått i RA och det som bäst förutsäger långtidsutfall.

Den farmakologiska behandlingen består av en rad olika mediciner som dämpar immunförsvaret och bromsar sjukdomsförloppet. De viktigaste läkemedlen är: kortison som har använts sedan 1940-talet, metotrexat som använts sedan 1980-talet och TNF hämmare som är s.k. biologiska läkemedel och introducerades i slutet av 1990-talet. Ett flertal andra biologiska läkemedel har tillkommit under senare år liksom målinriktade syntetiska bromsmediciner.

Remission

Att vara i remission betyder att sjukdomssymtomen är borta. Detta innebär emellertid inte bot av sjukdomen, utan en kortare eller längre period av symtomfrihet oftast framkallad av effektiv behandling. För patienter med RA betyder det i princip att det inte finns några svullna leder och ingen inflammation. Remission har inte varit ett realistiskt behandlingsmål förrän under de senaste åren. De finns olika remissionkriterier. De bygger på olika brytpunkter i tidigare nämnda aktivitetsindex alternativt en nyligen konstruerad ACR/EULAR definition. Långvarig remission (sustained remission, SR) definieras som remission inte bara vid ett besökstillfälle utan över viss tid. I denna avhandling definierar vi långvarig remission som remission i minst 6 månader och vid minst två på varandra följande mottagningsbesök. I denna sammanfattning redovisas remission enligt DAS28. Patienter som får diagnos och eventuellt behandling inom 6 månader från symtomdebut kallar vi ”tidig artrit” patienter.

Syfte

Det övergripande syftet med denna avhandling är att undersöka olika aspekter av remission, med speciellt fokus på långvarig remission (SR) bland patienter med RA. Mer specifikt:

Att undersöka: (i)hur vanligt SR är, när i tid patienter går in i långvarig remission och hur länge den varar (ii)om prognostiska faktorer kan förutsäga vilka patienter som har störst sannolikhet att gå i långvarig remission. (iii) möjliga positiva effekter av långvarig remission och jämföra med patienter som är i remission kortare tid än 6 månader. (iv)hur frekvensen av långvarig remission har ändrats över tid.

Patientmaterial

Alla arbeten bygger på data från två register där patienterna följs upp över lång tid.

I arbete I och II har vi använt ett regionalt register, SSATG (South Swedish Arthritis Treatment Group). Patienter med RA som startade behandling med TNF hämmare i Skåne och angränsande län från 1999 tom 2009 har studerats. De flesta patienter i SSATG är svårt sjuka och har haft sjukdomen i snitt 12 år vid behandlingsstart. Total 2416 patienter ingår i dessa studier.

I arbete III och IV analyserar vi data från SRQ (Svensk Reumatologis Kvalitetsregister), ett nationellt kvalitetsregister. En stor del av patienterna har registrerats i SRQ redan från sjukdomens början. I SRQ har hälften av patienterna med RA symtom duration under 2 år och ¼ del mindre än 6 månader från första symtom vid inkludering. Dessa patienter är i allmänhet inte lika sjuka som de i SSATG. Totalt 29084 patienter ingår i dessa studier.

Resultat

Av alla patienter med RA registrerade i SRQ var 71% i remission vid någon tidpunkt och 42% någon gång i långvarig remission. Strax under 50% av patienterna i SSATG var i remission någon gång och 16% i långvarig remission. Långvarig remission var mycket vanligare hos tidig artrit patienter.

De som uppnår långvarig remission gör det oftast under de första 2 åren, förekomsten ökar sedan långsamt och klingar av och är efter 5 år omkring 30%. Långvarig remission, även om den bara uppnås vid ett tillfälle under observationstiden, varar ofta i flera år. De prognostiska faktorer som är kopplade till långvarig remission är bland annat manligt kön, lägre ålder och mildare sjukdom med lägre sjukdomsaktivitet och bättre fysisk funktion. Att vara tidig artrit patient var starkt kopplat till långvarig remission. Bland patienter i SSATG var samtidig metotrexatbehandling kopplad till långvarig remission.

Patienter förbättrade sin fysiska förmåga (fick lägre HAQ) så länge som de var i remission. De fick även lägre HAQ jämfört med patienter som enbart var i remission då och då. Fler i långvarig remission återfick också full fysisk funktion (ingen inskränkning i HAQ) under remissionstiden.

Före 1992 var remission extremt ovanlig hos patienter med RA i Sverige. Därefter ökade antalet i remission successivt under åren fram till 2009. Bland patienter som insjuknade 2009 hade 45% nått SR efter 5 år. År 1990 uppnådde 0% av patienterna SR och år 1999 uppnådde 16% SR.

Slutsatser

Långvarig remission är ovanlig bland patienter med lång sjukdomsvaraktighet men är vanligare om behandling startar inom 6 månader från symtomdebut och med bibehållen fysisk funktion. Med tillkomst av snabb utvärdering och målstyrd behandling har möjligheten att uppnå långvarig remission ökat för patienter med nydebuterad RA.

Långvarig remission skall vara behandlingsmål för flertalet patienter med RA. Detta har fördelar för patientens fysiska förmåga utöver att uppnå remission då och då. När patienter startar behandling med TNF hämmare är det viktigt att behandla med metotrexat samtidigt om möjligt.

Många patienter uppnår fortfarande tyvärr aldrig långvarig remission även med modern behandling. Inom vården måste vi därför fokusera än mer på tidig diagnos, tät utvärdering, målstyrd behandling och även informera patienterna om livsstilsfaktorer och levnadsvanor som påverkar sjukdomsutvecklingen.

Vísindamiðlun - Ágrip á íslensku

Iktsýki (e. Rheumatoid arthritis, skammstafað RA), sem nefnist í daglegu tali liðagigt, er króníska sjálfsofnæmissjúkdómur. Í Svíþjóð er algengið hjá fullorðnum einstaklingum um 0.75%. Fólk getur veikst af RA hvenær sem er á lífsleiðinni og sjúkdómurinn er tvisvar til þrisvar sinnum algengari meðal kvenna en karla. Ekki er að fullu ljóst hvað veldur RA en um samspil erfða og umhverfisþátta er að ræða. Lífsstíll og venjur hafa mikil áhrif á sjúkdóminn og má í því sambandi nefna reykingar sem dæmi. Þær auka ekki aðeins líkur á að fólk veikist heldur hafa þær einnig áhrif á framvindu sjúkdómsins og meðferðarsvörun.

RA er fjölkerfasjúkdómur en veldur oft liðbólgum og sinaskeiðabólgum í höndum og fótum og algengt er að sjúklingar þjáist af morgunstirðleika, þreytu og slappleika. Án meðferðar leiðir sjúkdómurinn til skertar líkamlegrar færni, minna starfsþreks og minnkaðrar þátttöku í félagslegum athöfnum. Síðustu 20-30 árin hafa orðið stórtækar framfarir í meðferð RA og vaxandi fjöldi sjúklinga hefur óskert starfsþrek og getur lifað virku lífi.

Stærsta breytingin byggir á þeirri einföldu hugmynd að hamla bólgusvörunina sem veldur RA snemma, og halda henni stöðugt niðri. Þrjár meginreglur gilda í nútímameðferð: 1)Greina sjúkdóminn á byrjunarstigi. 2)Fylgja sjúklingnum vel eftir með tíðum skoðunum. 3)Aðlaga meðferðina að meðferðarmarkmiðum - þegar hægt er á meðferðarmarkmiðið að vera einkennalaus sjúklingur. Þetta markmið er ekki alltaf raunhæft og mikilvægt er að sníða meðferðina að þörfum hvers sjúklings í samvinnu við sjúklinginn sjálfan.

Þróun mælikvarða sem mæla sjúkdómsvirkni hefur átt stóran þátt í þessum framförum. Sjúkdómsvirkni er metin með samsettum mælikvörðum, liðskoðun og mælingu á bólgumiðlum í blóði, en álit sjúklings á sjúkdómsvirkni er tekið með í reikninginn. Til dæmis er DAS28 línulegur mælikvarði sem samanstendur af fjölda aumra og bólginna liða, sökki og áliti sjúklings á skalanum 0-100. Líkamleg færni er ákvörðuð með spurninglista (HAQ, Health Assessment Questionnaire). Hann inniheldur 20 spurningar sem meta ólíkar líkamlegar athafnir daglegs lífs. Þessi mæling er afar mikilvæg því líkamleg færni virðist hafa besta forspárgildið um langtímahorfur sjúklinga með RA.

Mismunandi bremsulyf eru notuð til að ná markmiðum meðferðarinnar. Mikilvægustu lyfin eru: Bólgueyðandi barksterar sem hafa verið í notkun í marga áratugi, metotrexate sem hefur verið notað síðan á níunda áratugnum og TNF-hamlandi lyf sem eru svokölluð líftækni lyf. Fyrstu lyfin komu á markað undir lok tíunda áratugarins, síðan þá hafa allmörg líftækni lyf komið á markaðinn.

Sjúkdómshlé

Sjúkdómshlé (e. remission) er ástand þar sem ekki ber á neinum einkennum sjúkdómsins, „hlé“ vísar til þess að þetta ástand sé ekki varanlegt og að sjúklingurinn sé ekki læknaður. Einfaldasta skilgreiningin á sjúkdómshléi tengdu RA væri þá að sjúklingur hefði ekki neinar liðbólgur og enga hækkun á bólgumiðlum í blóði. Þetta hefur þó ekki verið svona einfalt og sjúkdómhlé hefur ekki verið raunhæft meðferðarmarkmið fyrr en síðustu árin. Eldri skilgreiningar eru byggðar á hugmyndum gigtarlækna um sjúkdómshlé frá því fyrir um 20 árum og leyfa þónokkra virkni í sjúkdómnum. Engin hinna hefðbundnu skilgreininga sjúkdómshlés notast við tímamörk. Við höfum skilgreint langvinnt sjúkdómshlé (e. sustained remission) sem sjúkdómshlé í að minnsta kosti sex mánuði.

Tilgangur

Megintilgangur doktorsverkefnisins er að rannsaka sjúkdómshlé hjá sjúklingum með RA með áherslu á langvinnt sjúkdómshlé (LS).

Nánar: Að rannsaka algengi, tímasetningar og lengd LS. Að rannsaka mögulega forspárþætti LS. Að rannsaka hugsanlegan ávinning af LS. Að rannsaka hvernig algengi LS hefur breyst í gegnum árin.

Sjúklingar

Rannsóknin er byggð á gagnagrunnum þar sem sjúklingum er fylgt eftir yfir langt tímabil.

Í greinum I og II er notast við gögn úr gagnagrunninum SSATG (South Swedish Arthritis Treatment Group) sem stofnaður var af rannsóknarhópnum í Lundi 1999. Allir sjúklingar sem hófu meðferð með líftækni lyfjum á Skáni og í aðliggjandi lénum voru skráðir í grunninn. Við þessar rannsóknir notuðum við gögn frá öllum fullorðnum RA sjúklingum sem fengu meðferð með TNF-hamlandi lyfi fram til 2010 (n=2416). Flestir þessara sjúklinga voru slæm tilfelli sem illa gekk að meðhöndla og höfðu haft sjúkdóminn í 12 ár að meðaltali.

Fyrir greinar III og IV fengum við gögn frá SRQ (Svensk Reumatologis Kvalitetsregister), gæðaskrá sem heldur utan um RA sjúklinga á landsvísu (n=29084). Í þessa skrá hefur stór hluti sjúklinga verið skráður við sjúkdómsbyrjun. Helmingur hefur styttri sjúkdómslengd en tvö ár og einn af fjórum styttri en sex mánuði. Sjúklinga sem hafa fengið greiningu og meðferð á innan við sex mánuðum frá fyrstu einkennum köllum við sjúklinga með „byrjunarstigs RA“. Að meðaltali eru sjúklingar í SSATG með erfiðari sjúkdóm en sjúklingar í SRQ.

Niðurstöður

Af RA sjúklingum í SRQ uppfyllti 71% skilgreininguna á sjúkdómshléi á einhverjum tímapunkti og 42% upplifðu LS. Sambærilegar tölur voru 50% og 16% í SSATG. LS var mun algengara meðal sjúklinga sem greindust með RA á byrjunarstigi.

Flestir sem upplifa LS gera það á fyrstu tveimur árunum eftir að þeir veikjast, algengi LS eykst svo hægt næstu þrjú árin upp í 30%, síðan verður lítil breyting á algenginu næstu árin eftir það. Sjúklingar voru í LS í yfir sjö ár að jafnaði í SRQ og í meira en 5 ár í SSATG. Margir eru ennþá í LS við síðustu skráðu heimsókn.

Athugaðir voru forspárþættir fyrir LS við fyrstu skráningu í gagnagrunninn. Þeir þættir sem tengdir voru við auknar líkur á LS voru meðal annars; lægri aldur, karlkyn og mildari sjúkdómur auk betri líkamlegrar færni. Að greinast með RA á byrjunarstigi var mikilvægasti forspárþátturinn. Meðal sjúklinga sem voru í SSATG og meðhöndlaðir með TNF-hamlandi lyfjum var samhliða meðferð með metotrexate forspárþáttur.

Líkamleg færni sjúklinga batnaði á meðan þeir voru í LS og meira en hjá sjúklingum sem fóru einstaka sinnum í sjúkdómshlé en aldrei í LS.

Fyrir 1992 voru sjúkdómshlé afar sjaldgæf. Ef miðað er við árið þegar fólk veikist aukast líkurnar á LS jafnt og þétt fram til þeirra sem veikjast 2009. Tíminn frá sjúkdómsbyrjun að LS styttist líka jafnt og þétt á tímabilinu.

Ályktanir

Þegar mögulegt er skal það að ná og viðhalda sjúkdómshléi vera markmið við meðferð sjúklinga með RA. Langvinnt sjúkdómshlé eykur líkamlega færni sjúklinga umfram það þegar sjúkdómshlé næst bara öðru hverju. Þegar meðhöndlað er með TNF-hamlandi lyfjum skal ávallt leitast við að meðhöndla sjúklinginn samhliða með metotrexate.

Langvinnt sjúkdómshlé er sjaldgæft meðal sjúklinga með langt genginn sjúkdóm en það er mun algengara meðal sjúklinga með byrjunarstigs RA og fulla líkamlega færni. Með breyttum hugsunarhætti, þar sem sjúklingum er fylgt vel eftir með tíðum skoðunum, og með meðferðarmarkmiðum, hafa fleiri sjúklingar með RA á byrjunarstigi möguleika á langvinnu sjúkdómshléi.

Því miður er það þó ennþá svo að margir sjúklingar upplifa aldrei langvinnt sjúkdómshlé. Þeir sem sinna heilbrigðisþjónustu þurfa að leggja meiri áherslu á að greina sjúkdóminn snemma og fylgja sjúklingum vel eftir með stífum markmiðum. Mikilvægt er að upplýsa sjúklingin um meðferðina og markmiðin og benda á ávinning af lífsstílsbreytingum sem hafa áhrif á framvindu sjúkdómsins.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease mostly affecting small and medium sized joints, such as in the hands and feet and often symmetrically. It causes inflammation in the relatively acellular synovium leading to a hyperplasic somewhat invasive "pannus" that can cause bone and cartilage breakdown. At first the inflammation causes pain and limits the range of motion but with disease progression the structural damage causes loss of joint function. RA is a systemic condition with inflammation involving e.g. the respiratory, hematopoietic and cardiovascular system and can give rise to a wide range of symptoms. The expected lifespan of patients with RA is probably shortened by 4-10 years: This is due to increased risk of atherosclerosis and lymphoma as well as other comorbidities such as infections (1,2).

Epidemiology

RA affects around 0.5-1% of adults but with some regional variations and variations across ethnic groups and socioeconomic position (3–5). It is estimated to affect 0.77% of adults in Sweden, with incidence rates of 41 per 100,000 (5,6). In southern Sweden the prevalence of RA was estimated to 0.66% with an incidence of 50 per 100,000 (7). Women are more frequently affected than men with a prevalence of 0.94% vs 0.37% respectively in the same study (7). People in all ages can be affected but symptom onset is at mean 60 and median 61 years in Sweden (6).

The difference in incidence between the sexes has led to the suggestion that hormonal and reproductive factors might partly explain this. Oral contraceptives seem to reduce the risk of RA, but the studies on the effects of breastfeeding on RA have shown somewhat conflicting results (8). The most established environmental risk factors for RA are smoking and socioeconomic status or educational attainment (6,9,10). RA is a complex genetic disease, meaning that besides environmental factors several genes and chance act together in the pathogenesis. Having a family history for RA is the strongest known risk factor for developing the disease. RA seems to cluster in families with a concordance of about 12% in monozygotic twins and a two to fourfold increase in risk among first degree relatives to patients with RA (11,12)(13,14). This can only partly be explained by other known environmental risk factors (10). There is accumulating

evidence that presence of a certain genetic variation is associated with a subset of RA that is defined by the presence of antibodies to citrullinated protein antigens (ACPA), rheumatoid factor (RF) or both (15,16).

Diagnosis

The dominant features at diagnosis is joint and tendon sheath tenderness and swelling. This typically includes the wrists and adjacent tendon sheaths, the proximal interphalangeal (PIP) joints, the metacarpophalangeal (MCP) joints, and the metatarsophalangeal (MTP) joints. Still, the disease can present with involvement of only one or few joints and this presentation is not specific for RA. The list of other causes to be considered is long. Often patients have a preliminary diagnosis of undifferentiated arthritis (UA) for some time before they fulfil a formal diagnosis of RA. Classification criteria were developed for clinical research purposes in 1987 (Table 1) (17). These criteria have limited clinical value, especially early in the disease as some of the criteria (nodules, radiographic changes) reflect long standing disease.

A new criteria set was developed using cohorts of patients with early UA, the entry criterion is at least one swollen joint (

Table 2)(18). These criteria are more sensitive than the 1987 criteria, but less specific (19). Tests for RF and ACPA are important for the diagnosis and RF was included in the 1987 criteria, levels of RF and ACPA are also included in the newer criteria.

However, no diagnostic criteria exists and the diagnosis of RA is based on the clinical judgement of the treating physician.

Table 1. 1987 ACR classification criteria (17)

Rheumatoid arthritis is defined by the presence of 4 or more criteria. Criteria A, B, C and D must have been present for at least 6 weeks.

1987 American College of Rheumatology classification criteria for RA	
At least four of the following criteria	
A.	Morning stiffness >1h
B.	Arthritis of ≥ 3 joint areas
C.	Arthritis of hand joints
D.	Symmetrical arthritis
E.	Rheumatoid nodules
F.	Serum rheumatoid factor
G.	Radiographic changes

Table 2. 2010 ACR/EULAR classification criteria for RA(18)

Target population are patients who have at least 1 joint with definite clinical synovitis and with the synovitis not better explained by another disease. Scores for each of four domains are added. A score of ≥6 indicates RA.

2010 American college of Rheumatology classificatoin criteria for RA		
Domain	**Parameter**	**Score**
A. Joint involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (≥1 small)	5
B. Serology	Negative RF *and* negative ACPA	0
	Low positive RF *or* low positive ACPA	2
	High positive RF *or* high positive ACPA	3
C. Acute phase reactants	Normal CRP *and* normal ESR	0
	Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms	<6 weeks	0
	≥6 weeks	1

Course of RA

RA has been called “one of the most intractable, obstinate, and crippling diseases that can befall the human body” (20). The natural course of the disease is characterized by periods of lower disease activity and relapses but complete spontaneous remission has been so uncommon that is has been regarded as a medical curiosity (20). In early disease joint symptoms predominate with loss of function secondary to pain and swelling.

Stiffness is also pronounced, especially after inactivity and is often referred to as morning stiffness, typically lasting more than 1 hour. Extra-articular manifestations are seldom present early in RA. The synovium is the primary site for the inflammatory process in RA, and with disease progression the inflamed synovium becomes thickened, hyperplastic and oedematous and develops villous projections called pannus. Early joint erosions are associated with this proliferative pannus that is capable of invading bone and cartilage (Figure 1) (21). As the joints become deformed mechanical stress is added to the inflammatory process of joint erosion.

In patients with established RA the clinical challenge is different from that in early disease. Inflammation in the joint can still be present but the joint involvement can be dominated by deformities. Loss of function is both secondary to mechanical and inflammatory joint pain as well as deformities. In established RA extra-articular manifestations develop in up to 40% of patients (22). The more common ones include rheumatic nodules, keratoconjunctivitis sicca, pulmonary fibrosis, pleuro-pericarditis and cutaneous vasculitis (22). The subgroup of patients with RF are particularly at risk.

Other co-morbidities include osteoporosis and increased risk of infections (1). This is partly due to the disease itself and partly due to the treatment. The risk of lymphoma and lung cancer is increased among patients with RA but overall the risk for malignancies is not increased (23,24). Inflammation in RA affects the brain function with fatigue as a prominent symptom (16,25,26). Cardiovascular disease (CVD) is common and the level of atherosclerosis correlates with the level of systemic inflammation over time (27,28). CVD is the major cause of death in RA and patients with RA have had a shortened lifespan by 4-10 years (1,2). Modern treatment might have impacted this. In a recent nationwide Swedish study the relative risk of death was not increased in a cohort of RA patients with disease onset after 1996 compared with the general population (29). But even with the treatment available today, an excess mortality in the RA cohort was present 5 years after RA diagnosis (HR after 10 years since RA diagnosis=1.43). No clear trend towards lower excess mortality in patients diagnosed more recently was seen (29).

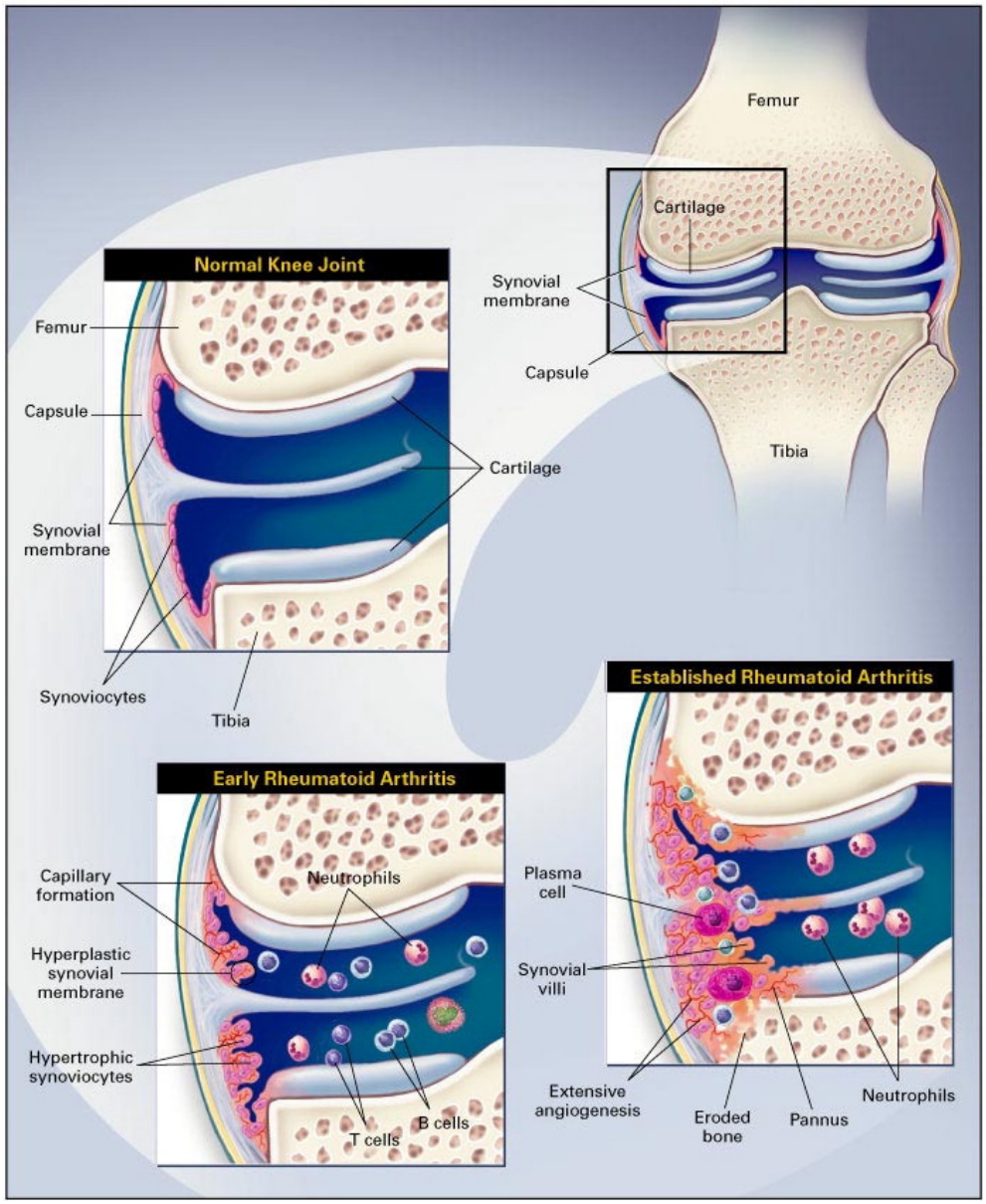


Figure 1. Pathogenesis of Rheumatoid Arthritis.
In the normal knee joint, the synovium consists of a synovial membrane and underlying loose connective tissue. In early rheumatoid arthritis, the synovial membrane becomes thickened because of hyperplasia and hypertrophy of the synovial-lining cells. An extensive network of new blood vessels is formed in the synovium. T and B cells infiltrate the synovial membrane. These cells are also found in the synovial fluid, along with large numbers of neutrophils. In the early stages of rheumatoid arthritis, the synovial membrane begins to invade the cartilage. In established rheumatoid arthritis, the synovial membrane becomes transformed into inflammatory tissue, the pannus. This tissue invades and destroys adjacent cartilage and bone. Reproduced with permission from Choy, Ernest H.S., and Gabriel S. Panayi. "Cytokine Pathways and Joint Inflammation in Rheumatoid Arthritis." New England Journal of Medicine 344, no. 12 (March 22, 2001): 907–16. Copyright Massachusetts Medical Society

Predicting disease course in the individual patient

RA can have a variable disease course from a very mild joint disease to a disease of physical disability, structural damage and increased mortality. The severity of these outcomes can be predicted to some extent in early RA. The presence of RF and/or ACPA has been associated with more severe disease, other predictors include older age, smoking, measures indicative of greater disease activity, extra-articular manifestations and bone erosions (30–33). Although indicative, none of these predictors, alone or in combination have been able to give a reliable prediction model for the individual patient. Physical function seems to be the most powerful predictor of mortality, followed by other patient reported outcomes (PROs) (34). Radiographic damage is a substantially weaker predictor of mortality, although an independent predictor of reduced physical function (31,34).

Trends in disease severity

The prognosis for patients with RA has become better. At least that is the perception among rheumatologists. Previously common complications of disease such as amyloidosis, C1 cervical subluxations, corneal melts and vasculitis with leg ulcers are now rarely seen. There is surprisingly little data to support this perception though. In a study from the Mayo clinic there was no decrease in the incidence of extra-articular manifestations in patients with RA diagnosed up to 1995, another study showed a dramatic decline in the incidence of rheumatoid vasculitis from 1994 to 2000 (22,35). There are data available from multiple centres on decreasing rates of hospital admission and RA related surgical procedures, and there is slowly accumulating data on milder radiographic progression, better health status, lower disease activity and improved mortality (36–45).

There seems to be a trend towards a lower disease activity at diagnosis. In a study of patients entered into the Norfolk Arthritis Register in the UK from 1990 to 2008 the baseline disease activity declined over time (46). A similar trend was seen when studying sub cohorts from different periods in Nijmegen, the more recent cohorts had lower disease activity, both at baseline as well as over the first 5 years of their disease (43). In a ten year study from the Norwegian Antirheumatic Drug Register covering the years between 2000 and 2010, a decline in the number of swollen joints, in serum markers of inflammation and pain at start of first treatment was observed (47). There was also a dramatic trend towards initiation of treatment earlier in the disease course to a median one month from over 10 months (48).

Outcome measures

> The primary goal of treating patients with RA is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and participation in social and work-related activities (Smolen, *Ann Rheum Dis*, 2016 (49))

Measuring disease activity and adjusting the treatment accordingly optimises outcomes in RA (50). On the individual level, consequences of disease as well as severity and disease activity can be evaluated using several quantitative measures. A core set of disease activity measures were recommended in 1993, based on the ability to predict serious outcome and on sensitivity to clinical change (51). These are readily available for the clinician in routine care (Table 3). The core set measures can be used separately or in different combinations through composite disease activity indices (DAI, Table 4). Some of the core set measures are based on patient reported outcomes (PROs) and reflect the patient's perspective. These include pain, patient's global assessment of disease activity (PtGA) and patient's assessment of physical function. There is high level of evidence that these PROs correlate both cross-sectionally and longitudinally with DAI (52).

Table 3. ACR disease activity measures for RA clinical trials: core set (51)

	Disease activity measure
1.	Tender joint count (TJC)
2.	Swollen joint count (SJC)
3.	Patients´s assessment of pain.
4.	Patient´s global assessment of disease activity (PtGA)
5.	Evaluators global assessment of disease activity (EGA)
6.	Patient´s assessment of physical function
7.	Acute-phase reactant value (CRP or ESR)
8.	Radiography*
*For special Clinical Trial settings such as trial duration ≥ 1 year and agent being tested as a disease modifiing anti rheumatic drug (DMARD).	

Formal joint count is the most specific measure to assess RA both in clinical trials and in clinical care. Joint tenderness is pain that is induced by pressure at examination of some joints such as the MCP or wrist joints. Pain on motion may be substituted for pressure at examination for the shoulder and hip joints. Joint swelling is a soft tissue swelling detectable along the joint margin. Fluctuation is a key feature of swollen joints, thus bony enlargements and deformities are not considered to be swelling. A standard joint count, limited to 28 joints (includes MCP and PIP joints, wrists, elbows, shoulders and knees) is most often used and provides comparable information as more time consuming joint examination methods (53). Although not without limitations,

especially intra- and inter observer reproducibility, swollen joint count (SJC) is one of two core set measures that consistently is associated with radiographic progression or joint destruction, the other one being erythrocyte sedimentation rate (ESR) (54,55). Tender joint count (TJC) is on the other hand related to actual disability (56).

Patient's assessment of pain is done on a horizontal visual analogue scale (VAS, usually 100mm) or a Likert scale from 0-10 indicating the current level of pain, between "No pain" and "Worst thinkable pain". Patient global assessment (PtGA) and evaluator global assessment (EGA) are similarly scored on a 100mm VAS scale. When assessing PtGA there are variations in wording/phrasing of the question asked ranging from measuring Global health (GH) to disease activity (57). In the ACR core set recommendations the following question is considered acceptable: "Considering all the ways your arthritis affects you, mark 'X' on the scale for how well you are doing"(51). This wording is in line with the Swedish version of the question which also includes the phrase "during the last week" (Appendix B). PtGA is a component of many DAIs but when used alone lacks validity and correlates poorly with DAIs such as the DAS28 (see below) (58,59). In Sweden EGA has traditionally consisted of applying one of five disease states, remission, low, mild, high, maximum, rather than a continuous VAS scale.

There is often a considerable discordance between PtGA and EGA measures. (60,61). In general PtGA correlates better with TJC than SJC but EGA correlates equally well with TJC and SJC.

As mentioned above ESR correlates with joint progression over time. But ESR is often confounded by other factors than disease activity, it increases with age and is often higher in women (59). C-reactive protein (CRP) is a more reliable and direct measure of the acute phase response and less confounded by other factors than ESR.

Measures of physical function and disability

Patient´s assessment of physical function is one of the core set measures. Functional ability can be divided into three levels; level of body or body part, the whole person, and the whole person in a social context. Disability involves dysfunctioning at one or more of these same levels: impairments, activity limitations and participation restriction (62). Even though RA causes dysfunction at all these levels the participation restriction is mostly secondary to the other levels, therefore when measuring functional status in RA the focus is on physical function at a body level.

Developed in 1978, the Health Assessment Questionnaire Disability Index (HAQ-DI) is the golden standard for measuring bodily functional status in RA, it is usually referred to as "the HAQ". In the original or "Full HAQ" some social aspects such as sex, psychological discomfort and social cost (employment, transportation) were included

but the HAQ-DI, consisting of 8 categories of physical activities of daily life, is now exclusively in use. These 8 categories make up the HAQ-DI; dressing, arising, eating, walking, hygiene, reach, grip and usual activity. Each category contains at least 2 specific component questions. For each item, there is a 4 level difficulty scale that is scored from zero to 3, representing normal (no difficulty) (0), some difficulty (1), much difficulty (2), and unable to do (3). The highest component score in each category determines the score for the category (63). To accurately represent underlying disability, dependence on aids or help increases a lower score to the level of 2. The 8 category scores are averaged into an overall HAQ-DI score on a scale from zero to 3, zero indicating no disability or full physical function, 3 indicating complete disability. The scale has 25 possible values and is not truly continuous (64).

HAQ-DI is highly sensitive to change in disability, with minimally clinical important difference for scores around 0.22, although estimates range depend on populations (65). It is limited at the normal function range and has a floor effect, demonstrated by patients with relative little difficulty who cannot improve in score despite clinical improvement (66).

The normative values of HAQ-DI have been studied in a population in central Finland. Overall the mean HAQ-DI was 0.25 with approximately one-third reporting some disability (HAQ-DI>0) (67). The disability curve was flat until age 50 years; subsequently, it increased in an exponential manner (Figure 2).

In Sweden a translated and slightly modified version of the HAQ-DI has been used since 1988, it has been validated and tested for reliability (68). It includes the original 20 questions assessing specific activities of daily living but instead of the 4-point Likert-scale it has a 6-point scale including the use of aids and help, like the HAQ-DI, dependence on aids or help increases a lower score to the level of 2 (Appendix B).

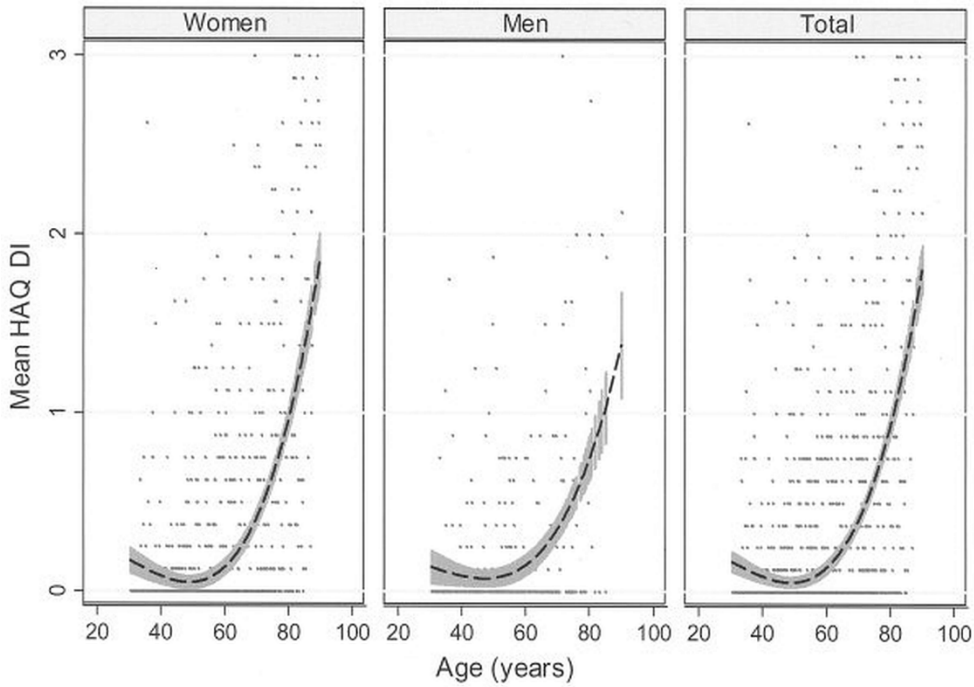


Figure 2. Progression of the mean HAQ-DI with age.
The curves with their 95% confidence bands were fitted using fractional polynomial modification of ordinary least squares regression. The decline indicated by the left side of each curve is not statistically significant because of the wide confidence band. Reproduced with permission from Krishnan, Eswar, Tuulikki Sokka, Arja Häkkinen, Helen Hubert, and Pekka Hannonen. "Normative Values for the Health Assessment Questionnaire Disability Index: Benchmarking Disability in the General Population." Arthritis & Rheumatism 50, no. 3 (March 2004): 953–60. With permission from Wiley.

There have been different cut points used defining full physical function and HAQ-DI ≤0.5 is common. In the current investigation we have used HAQ-DI =0 since a higher value by definition indicates disability.

Some shorter versions of HAQ have been developed primarily to shorten patient and provider time commitment (69). The most used version is probably the Modified health assessment questionnaire (MHAQ). MHAQ consists of eight items, one from each of the 8 HAQ-DI categories (65). The benefits of a shorter version come at the price of loss of sensitivity and loss of sensitivity to change (69). From now on the HAQ-DI will be referred to simply as "HAQ".

Disease activity indices

Combining core set measures to a DAI gives a measuring instrument that is more reliable and more responsive to change than separate measures. These composite measures are today recommended in both clinical trials and clinical practise in RA (52).

Table 4. Composite measures of disease activity, including joint counts, and ACR-EULAR remission criteria.
Adopted from The Lancet, Volume 388, Issue 10055, 22–28 October 2016, Pages 1984, Copyright (2016), with permission from Elsevier.

	Components	Cut-points			
		Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28-ESR	TJC, SJC, ESR, PtGA (in mm)	<2.6	2.6 to 3.2	>3.2 to ≤5.1	>5.1
DAS28-CRP	TJC, SJC, CRP (in mg/L), PtGA (in mm)	<2.6	2.6 to 3.2	>3.2 to ≤5.1	>5.1
SDAI	TJC, SJC, EGA and PtGA (both in cm), CRP (in mg/dL)	≤3.3	>3.3 to 11	>11 to ≤26	>26
CDAI	TJC, SJC, EGA and PtGA (both in cm)	≤2.8	>2.8 to 10	>10 to ≤22	>22
ACR-EULAR remission	Index: SDAI, CDAI; Boolean: SJC, TJC, PtGA in cm, CRP (in mg/dL)	SDAI ≤3.3, CDAI ≤2.8, Boolean all ≤1	..	..	..

PtGA= patient global assessment of disease activity; mm in DAS28, CDAI, SDAI; cm in Boolean. ACR=American College of Rheumatology. EULAR=European League against Rheumatism. DAS28=disease activity score using 28 joint counts. SDAI=simplified disease activity index. CDAI=clinical disease activity index. TJC=tender joint count (of 28). SJC=swollen joint count (of 28). ESR=erythrocyte sedimentation rate (in mm). CRP=C-reactive protein.

DAS28-ESR calculated according to the following equation:

$0.56 \times \sqrt{(TJC28)} + 0{\cdot}28 \times \sqrt{(SJC28)} + 0{\cdot}70 \times \log_e(ESR) + 0{\cdot}014 \times GH.$

DAS28-CRP calculated according to the following equation:

$0{\cdot}56 \times \sqrt{(TJC28)} + 0{\cdot}28 \times \sqrt{(SJC28)} + 0{\cdot}36 \times \log_e(CRP + 1) + 0{\cdot}014 \times GH + 0{\cdot}96.$

SDAI calculated according to the following equation: $TJC28 + SJC28 + PtGA + EGA + CRP.$

CDAI calculated according to the following equation: $TJC28 + SJC28 + PtGA + EGA.$

Most of the DAI include some PROs, a joint count and sometimes an acute phase reactant. Some aggregate PROs in a composite score, such as the RAPID, eliminating the need for a physical examination. RAPID correlates well with other DAIs but has not been evaluated with regard to long term outcomes (54,59). The following measures all have good to excellent reliability evidence and are recommended by the EULAR and ACR: disease activity score with 28-joint counts (DAS28), simplified disease activity index (SDAI) and clinical disease activity index (CDAI) (52,59). These all include joint and PtGA or GH (Table 4). There is almost a linear relationship between these DAIs over time and damage progression and disability (70).

Cut-points can indicate disease activity "state", remission, low, moderate and high activity.

DAIs can also be used to measure response to given treatment. A "response" is a change in score cut-points for various response levels, such as the EULAR response (good response, moderate response, no response) (71). The ACR response criteria (ACR20, ACR50, ACR70) is not based on a continuous composite measure and cannot measure "state" and cannot be used in clinical practice. It is often used to measure response in clinical trials (52).

Disease activity score with 28-joint counts (DAS28)

The DAS28 is often considered as the golden standard for assessing disease activity in RA. It is based on another DAI, DAS that used the Ritchie articular index, a 44 joint count. From 1985 all patients with an early RA in Nijmegen in the Netherlands, were assessed regularly and physician judgment of disease activity level was used as an external standard for DAS development (72). The DAS28 was later developed using similar methods as it is more feasible for regular clinical use (73). DAS28 is based on TJC and SJC, PtGA (or GH) and ESR and calculated according to a complex equation (Table 4). Both these DAI have been extensively validated and are endorsed by the ACR and EULAR for RA in clinical trials (52). Disadvantages in clinical practice include the need for a blood sample and a complicated mathematical calculation of the composite score. Furthermore, tender joints weigh more heavily than swollen joints, and it is possible to achieve a very low score despite several swollen joints.

Simple disease activity index (SDAI) and Clinical disease activity index (CDAI)

The SDAI was based on a DAI for reactive arthritis (DAREA) (74). Calculation of the SDAI is a simple linear sum of the outcome parameters, TCJ, SJC, PtGA (0-10cm), EGA and CRP (mg/dL) (Table 4). It was validated using DAS28, ACR20 and HAQ scores for correlation and using physician judgement (74). Based on the SDAI, the CDAI was developed as a simple calculation of disease activity for the use in the clinic at point of care, without the need for any laboratory measurement. The CRP is therefore removed, otherwise it is analogues to SDAI. They include both PtGA and EGA and this adjusts for the often observed discrepancy between these measures (see above). The SDAI and CDAI are endorsed by the ACR and EULAR for disease activity measurements in clinical trials and by EULAR for patient monitoring (52). These instruments were designed not to replace DAS28 but to be simpler and provide options for different environments.

Remission

> The term 'complete remission' implies the total absence of all articular and extra-articular inflammation and immunologic activity related to RA (Pinals, Arthritis Rheum, 1981 (75)).

The term remission has been used in RA for long time. In his Nobel lecture in 1950 Dr. Hench points out that a complete remission in RA is so uncommon that it is regarded as a medical curiosity (20). He discussed different aspects of remission such as asymptomatic remission, a transient remission, a temporary remission or a complete remission. Without providing any definition of remission in his talk, Dr Hench clearly stated that remission is not cure, only absence of disease activity. A standardized definition of "complete clinical remission" was first suggested in 1981 by the American Rheumatism Association (ARA) to "dispel the vagueness and confusion" that accompanied the term remission (75). Unlike other remission criteria in RA it included a time definition, the clinical criteria should be fulfilled for at least 2 consecutive months. Some of the requirements included measurements not included in the "core set"; tendon sheath swelling, fatigue and morning stiffness (75). Therefore and due to the fact that the definition was very stringent it has not been widely used.

With the development of DAIs, a disease activity has increasingly been considered a continuum with remission as a state at the very end of it (76). A cut-off point in a DAS score for RA, corresponding to fulfilment of the ARA criteria for remission was determined. This was achieved with receiver operating characteristic (ROC) analysis on a sample of patients from the Nijmegen RA cohort mentioned above (77). The optimal cut-off for DAS was determined at 1.6 (78). The optimal cut point for DAS28 was derived mathematically from this and was found to be 2.66, conservatively rounded off at 2.6 with both sensitivity and specificity for the ARA criteria at 87 (77). The original calculations for DAS were published in 1996 and both DAS and DAS28 cut-off points are therefore based on judgements from times when remission was thought to be rare (79). Almost 10 years later the levels for disease activity were presented for SDAI. This time rheumatology "experts" classified cases as remission, low, moderate or high disease activity and SDAI scores were mapped to these ratings. The cut point for remission was determined to be 3.3 and the results were validated using observational cohorts (79). The CDAI cut-off points (2.8) reasonably reflect the absence of CRP in that score. The difference of 0.5 corresponds to the upper level of CRP (in mg/dL) in patients near remission (80). Using Kappa Statistics the agreement between SDAI and CDAI in classifying remission is shown to be almost perfect (80).

Remission should be a state that can be achieved for a significant proportion of patients both in clinical trials and daily practice. But the definition should be strict enough not to allow patients with residual activity to go untreated. With the evolving treatment approach in RA with more and more patients in remission, it has become clear that the

perception of remission today is not the same as it was in 1996. DAS28 remission probably better represents low or minimal disease activity rather than true remission, as mentioned earlier multiple joints can remain swollen below the score of 2.6 (78,79,81–83).

Given these concerns an ACR and EULAR committee proposed a definitions in 2011 that should be stringent enough to define true remission. Different core set measures were used to construct candidate definitions of remission. The ability to predict later radiographic and functional outcomes were tested. The committee proposed a Boolean-based (true/false) criteria set including a joint count, CRP and PtGA (Table 4). Patients in remission are allowed to have a maximum of one joint with residual tenderness or swelling (84). The committee proposed the use of SDAI remission as an index based alternative in clinical trials and the use of CDAI in clinical practice where CRP is not always available (84).

Sustained remission

Except for the ARA-criteria none of the remission criteria account for time, and the majority of published studies report remission rates at a single time point. Given the chronicity of the disease and possible long-term benefits of remission a definition including time might give a more favourable long term outcome, being in remission over time should be better than at one time point. In the latest update of the EULAR recommendations the treatment target has moved forward from a state of clinical remission to maintenance of remission (49). There is no universal definition of sustained remission (SR) so a minimum of 6 months is mentioned in the recommendations. In studies on SR, mostly observational, the time frame varies from 6 to 9 months or 2 consecutive visits, 12 months apart (85,86). In a clinical trial remission at both 26 and 39 weeks after treatment start was called SR even though it was only sustained for 13 weeks (87). Range of outcome measures have also been used, both DAI and the ACR/EULAR criteria, combined with these different time frames.

Frequency of sustained remission

The frequency of SR depends on the definition and setting. The longer the time in remission required to fulfil the definition the fewer patients will be defined in SR. SR is more easily achievable early in disease and in clinical trials. The DAI used affects the frequency as well, the ACR/EULAR criteria is very strict and much lower remission rates are reported when applied compared to the DAS28 remission criteria, with the SDAI and CDAI in between (88,89). In studies focusing on patients treated with anti-tumour necrosis factor antibody (anti-TNF), the frequency was high in the stricter setting of a clinical trial, where 38% of patients achieved DAS28 6 month SR in the

HONOR study (90). The frequency was on the other hand low in an observational cohort study in the Corrona registry (7.9%) where SR was defined as remission on two consecutive visits (91). Similarly 12% reached sustained clinical remission or remission in ≥ 3 consecutive assessments during 5 years in a primary-care-based inception cohort of patients in the United Kingdom (Norfolk Arthritis Register, NOAR) (92). The authors defined remission as no tender or swollen joints out of 51.

The highest frequencies of SR are achievable early in disease. In a clinical practise in Finland, all consecutive patients between 2008 and 2011 with RA diagnosis were analysed at 3 and 12 months after starting treatment. DAS28 SR was achieved in 57% of patients and Boolean SR in 16% (93). In a two year Dutch intervention study on patients with high risk of developing persistent arthritis (tREACH) 57% reached SR, defined as DAS<1.6 on two consecutive visit 3 months apart (94). All patients received early intensive treatment. In another two year Dutch study, comparing different treatment strategies in early RA, up to 88% of patients reached DAS28 SR for at least 24 weeks over the course of the study (95). In a five year study in Denmark, over 25% of patients were in sustained ACR/EULAR remission over three years after early and strict synovitis suppressive treatment (96). In a two year study in Norway 20% reached a strict criteria of SR, defined as DAS less than 1.6 at 16, 20, and 24 months; no swollen joints at 16, 20, and 24 months; and no radiographic progression between 16 and 24 month (97). All patients had early RA and were treated with a tight control strategy.

Once remission is seen on two subsequent visits the chance of remaining in remission becomes much higher. The escape from remission is highest after one visit, of all patients in remission in the BRASS registry only 41% were still in remission at the next visit (86). The longer and the better a good clinical state is maintained, the greater the likelihood of remaining in that state. In the BeSt study the probability of a next DAS ≤2.4 3 months after a first DAS ≤2.4 was 74%. The probability increased to 85% after two preceding DAS ≤2.4 and to 88–97% after one to two preceding DAS<1.6 (98).

Predictors of sustained remission

It is important to be able to identify individual factors that predict disease persistency and severity as well as response to given treatment. SR is possibly the optimal outcome of treatment so studying which demographic or clinical factors predicts SR can help guide optimal treatment strategies. Most studies are observational and methods used usually include logistic regression models, sometimes combined with survival analysis (Cox-regression) including covariates. Results are therefore given as odds- or hazard ratios.

Clinical factors negatively associated with SR in the NOAR registry mentioned above were TJC (OR 0.94) and HAQ (OR 0.59) as well as comorbidities; obesity, hypertension and depression (92). Females had lower odds of reaching SR (OR 0.47)

in this registry. This was the case in another multicentre cohort in the United Kingdom where being female (OR 0.38) and having shorter symptom duration at treatment start (OR 3.15) as well as lower TJC (OR 3.73) were associated with SR (99). In a small Korean study HAQ was found to be an independent predictor of SR (OR 0.30) after adjusting for several clinical and demographic covariates (100). The time from symptom onset to diagnosis and treatment start is associated with SR. In a study on the Nijmegen cohort the time-to-remission emerged as the most important predictor of SR (OR 0.91 per month), after adjusting for several covariates (101). This means that the chance of SR decreases with the odds 0.91 with every month that goes without remission. Disease duration of more than 5 years at the start of a non-biologic DMARD was negatively associated with CDAI SR (OR 0.61) but not DAS28 SR in the CORRONA registry in North America (91). The researchers were unable to calculate DAS28 in many patients so the CDAI SR group was three times bigger, which might explain the difference. Fatigue was a predictor of SR (OR 0.32) as well as prednisone (0.42) and methotrexate (MTX, OR 2.04) use. M-HAQ was not associated with SR in this study.

A meta-analysis on the outcome DMARD-free SR revealed that symptom duration is independently associated with a reduced chance of this remission; with HR 0.989 per week increase in symptom duration (102).

There are some observational studies that have looked specifically at predictors of SR at the start of an anti-TNF treatment. In these studies several factors have been identified as candidate predictors for SR. In the study from the CORRONA registry, separate analysis were done on anti-TNF initiators (91). Disease duration of more than 5 years was negatively associated with CDAI SR (OR 0.90) but not DAS28 SR. Female sex was associated with DAS28 SR (OR 0.43) but not CDAI SR. Baseline disease activity and prior anti-TNF use were negatively associated with SR but concomitant MTX was positively associated with both CDAI and DAS28 SR with odds ratio for DAS28 SR being 2.83. In a small Irish study, TJC (OR 0.91) and increasing age (OR 0.94) was associated with SR (103). In a study on patients in the ABioPharm cohort in Canada, early remission (<16 weeks, OR 1.88) was associated with DAS28 SR as well as baseline EGA (0.80), while TJC (OR 0.96) was associated with CDAI SR and obesity (OR 0.30) with ACR/EULAR SR after excluding CRP from the criteria (104). A meta-analysis including this and two others studies with focus on the impact of sex on SR in anti-TNF initiators, showed that female sex reduced the likelihood of achieving SR (85).

In summary, a number of candidate predictors for SR have been identified including lower age, male sex, shorter disease duration, and lower HAQ, TJC and disease activity at baseline. MTX usage both as first DMARD and as concomitant medication with anti-TNF treatment is positively associated with SR. Although always included in the

predictive models, more objective measures such as SJC and inflammatory markers do not predict SR as well.

Benefits of sustained remission

There is still a question whether being in remission over longer period of time has any proven benefits over occasionally reaching remission or being in a steady state of low disease activity. Optimally, SR would reduce radiographic joint destruction, improve physical function and PROs as well as normalize comorbidities and survival. If so, remission is only the first goal in a treat-to-target approach and the maintenance of remission another.

There is some evidence that SR decreases joint damage. In a post hoc analysis of data from the PREMIER trial, patients that reached remission (SDAI, CDAI or DAS28) at 12 months and sustained this state at 24 months were analysed (105). There was a virtual arrest of progression of radiographic scores at the group level in patients in SR and patients being in remission for longest time before 12 months had the lowest radiographic scores. In a study on patients selected from the BRASS cohort, patients with longer time in remission, irrespective of DAI used, were less likely to have progressive radiographic joint damage (106). The few patients that had CDAI remission that stretched over 3 visits had no visible radiographic progression. In the Swedish BARFOT study, radiographic joint damage at 8 years was less pronounced in patients in SR irrespective of DAI used (107). This indicates that the maintenance of remission is more important than the DAI used.

When analysing those patients that responded well to MTX in the SWEFOT trial the patients who were in DAS28 remission at every visit up to and including a 2-year follow-up showed at least equal radiographic progression to patients not in remission, but there was no difference either in functional status between those that progressed and non-progressors (108). The mean HAQ decreased from start of remission and showed a linear trend over 23 weeks regardless of DAI used.

Even more relevant than inhibiting joint damage is maintaining physical function. Using a large sample of patients from several clinical trials researchers in Vienna showed that physical function continues to improve over time when remission is maintained (109). After 24 weeks of DAS28 SR about 60% had full physical function compared to 40% at remission start. A Dutch study evaluated long-term outcomes in patients with early RA after 10 years of targeted treatment (the BeSt study), aiming at low disease activity, DAS $\leq$ 2.4 at every 3-month visit (110). More than half where in remission, the mean HAQ was 0.57 indicating good physical function, clinically relevant radiographic damage was limited and mortality rate had normalized.

The effect of remission on mortality was studied in the NOAR early arthritis cohort (111). Patients with UA, were assessed at 1, 2 and 3 years, and by the third year ¾ had fulfilled the ACR criteria for RA. Patients that experienced remission at one occasion

during the first 3 years showed a 27% relative reduction in the risk of all-cause mortality. The number of assessments in remission was associated with a proportional decrease in mortality risk (HR 0.85), meaning that longer periods of remission give lower mortality. The time to first remission was also associated with a decreased risk of death and when first remission was not reached until the third year no advantage in survival was noted. The mortality rates of patients in DMARD-free sustained remission have also been compared to the general Dutch population in a cohort from the Leiden Early Arthritis Clinic (112). Here remission was defined as persisting absence of synovitis for at least 1 year after cessation of therapy. Patients that achieved remission within 3 years had reduced mortality compared with patients without remission and patients who achieved remission at any point as well. Compared to the general population, patients who achieved remission within 3 years or were in remission during the total follow up time did not have increased mortality.

In summary SR seems to benefit patients with evidence for decreased joint damage, better physical function and possibly reduced mortality.

Treatment

The development of different treatment strategies has changed the whole concept of RA from the historically chronic persistent disease course to the target of SR. The main idea driving this alteration is the early and consistent reduction in inflammation (16). Although the early immune pathways implicated in RA are still unclear, specific molecular mechanisms involved in the pathogenesis of the disorder should be targeted to reduce inflammation. Figure 3 illustrates these changes. For little more than 30 years ago few therapeutic agents existed and for those that existed the optimal dosing had not been clarified (113). The approach was dominated by the so called therapeutic pyramid where available potentially effective therapies were started late in the course of the disease because of fear of toxicity.

We have not reached the stage of 'induction' treatment in daily clinical practice. Most of our patients in the clinic today with established RA have been treated according to stage 2 (Figure 3), that is treatment targeted at low disease activity.

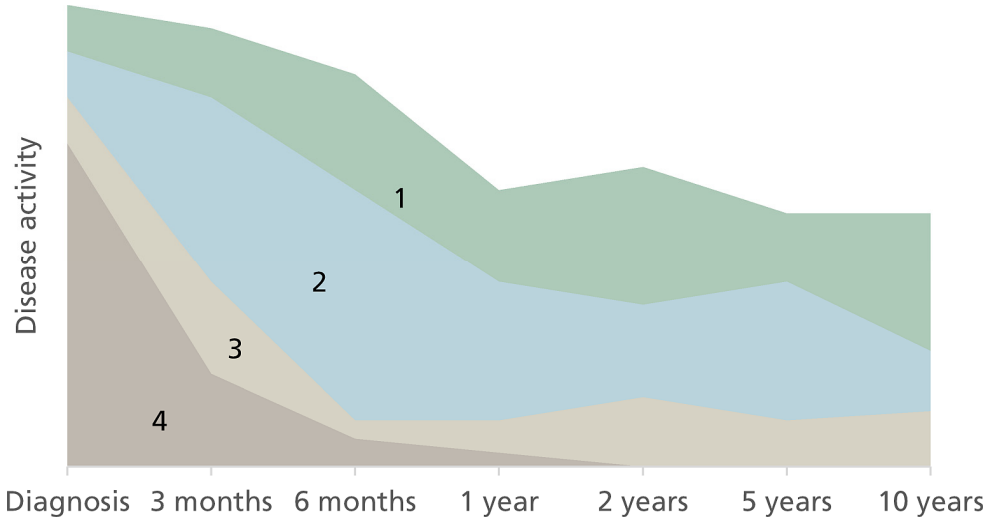


Figure 3. The concept of RA disease course and outcomes with the development of treatment strategies.

1.

'Historically' chronic persistent disease course

- Sustained disease activity
- Sustained arthritis-related symptoms
- High risk of joint destrucion
- Premature mortality

2.

Treatment targeted at low disease activity

- Low disease activity at some timepoint(s)
- Sustained residual disease activity
- Lower level of arthritis-related symptoms
- Lower risk of joint destruction
- Lower risk of loss of function
- Lower risk of premature mortality

3.

Early treatment targeted at sustained low disease activity

- Early suppression of disease activity
- Prolonged periods of low disease activity/remission
- Possible therapy reduction
- Sustained very low level of arthritis-related symptoms and improved health status
- Absence/low risk of joint destruction
- Absence/low risk of loss of function
- Improved survival

4.

'Induction' treatment targeted at sustained remission

- Rapid resolution of disease
- Prolonged periods of remission
- Therapy reduction
- Possible therapy discontinuation and sustained drug-free remission
- Sustained absence of arthritis-related symptoms and normalized health status
- Absence of joint destruction
- Normalized function
- Normalized survival

Adopted from Therapeutic Advances in Musculoskeletal Diseases, Ajeganova, Sofia, and Huizinga Tom. "Sustained Remission in Rheumatoid Arthritis: Latest Evidence and Clinical Considerations." Therapeutic Advances in Musculoskeletal Disease, August 2, 2017. Copyright, with permission from SAGE Publications.

The changes in management of RA have been driven by: a) the development of reliable tools for assessing disease activity and outcome, b) new diagnostic criteria and the appreciation of early diagnosis and c) early start of conventional synthetic disease-modifying antirheumatic drugs (csDMARD) with or without glucocorticoids (GC), d) recognition of MTX as powerful anchor drug, e) development of new biologic DMARDs (bDMARDs) (49,50). In addition, the definition of remission as a

treatment target and the application of the 'treat-to-target' recommendations has proven to be the most successful treatment strategy to date (16,49,70,114).

The TICORA study published in 2004 was the first randomized study to show how aiming at a defined treatment goal improved the effect of treatment (115). At two teaching hospitals in Glasgow patients with disease duration of less than 5 years were randomly allocated to either intensive management (treat-to-target) or routine care. The intensive group was seen monthly and underwent predefined escalation of therapy (per protocol) if they had not achieved the goal of DAS ≤ 2.4. Compared with routine care patients in the treat-to-target group were more likely to have a good response or be in remission and the mean fall in disease activity score was greater (Figure 4).

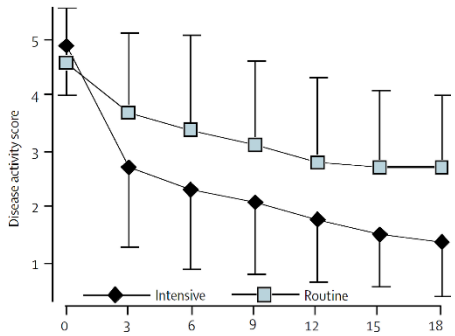


Figure 4. The TICORA study
Intensive treatment versus routine care. Months on the x axis. The primay outcome of a mean fall in disease activy score was alredy reached after 3 months of intensive treatment. This approach had no additional cost. Reprinted from The Lancet, Volume 364, Issue 9430, Catriona Grigor,Hilary Capell,Anne Stirling,Alex D McMahon,Peter Lock,Ramsay Vallance,Duncan Porter,Wilma Kincaid, Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial 263–69 July 2004, Pages 1984, Copyright (2004), with permission from Elsevier.

In Sweden national treatment recommendations date back to 2000 and have included the goal of clinical remission since the mid- 2000s (116,117). EULAR developed a first set of recommendations for the management of RA in 2010, these have been updated in 2013 and 2016 (49,114,118). EULAR has also developed recommendations for management of early arthritis in 2007, these were updated in 2016 (119,120). These recommendations address the use of GC, csDMARDs, bDMARDs, targeted synthetic DMARDs (tsDMARDs) and most recently biosimilars. The general 'tight-control', 'treat-to-target' approach to the patient with RA is shown below (Figure 5). The 'shared decision model' in RA involves shared decision-making between the physician and the patient and encompasses: information on the disease and its risks, the disease assessment methods, decisions on the therapeutic target and the potential means to reach the target, and discussions on the balance between benefits and risks of different therapies (49,121).

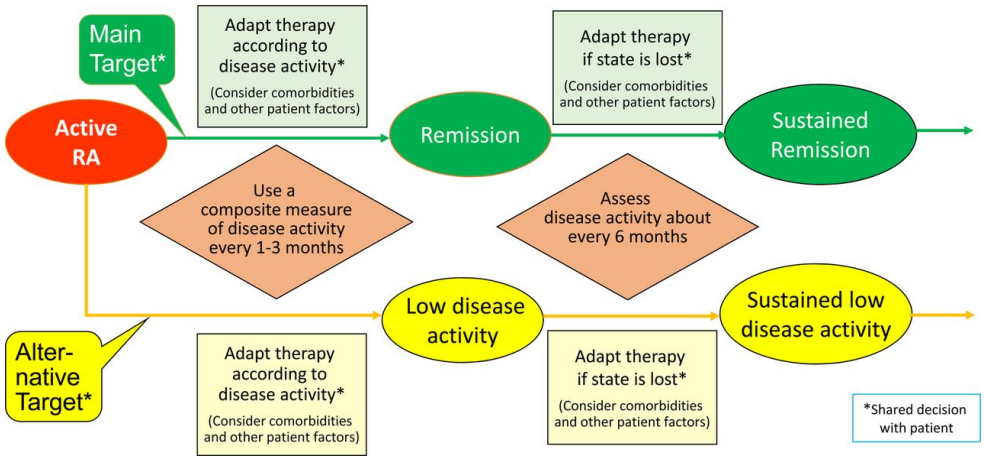


Figure 5. Algorithm of treating RA to target
The main target is remission and SR. An alternative target for patients with established RA is low disease activity and sustained low disease activty. The principle is to have a target, measure disease activity regularly (every 1-3 months), adapt therapy according to disease activity. When the target is reached the disease activity should be assessed regularly but not as often. Reproduced from Annals of the Rheumatic Diseases Smolen, Josef S., Ferdinand C. Breedveld, Gerd R. Burmester, Vivian Bykerk, Maxime Dougados, Paul Emery, Tore K. Kvien, et al., 75, 3-15, copyright 2016 with permission from BMJ Publishing Group Ltd.

Conventional synthetic DMARDs and glucocorticoids

RA was the first disease to be treated with 'Compound E' at the Mayo Clinic in 1948 (122). Responses were dramatic with more than 50% drop in ESR in all patients within 3 months. However despite rapid onset and other benefits of GC their toxicity soon became apparent. Traditionally low dose (≤ 7.5mg prednisolone/day) to moderate dose GC has been used alone or in combination with other DMARDs, and as a bridging therapy when initiating, pausing and switching between therapies. Currently GC are often used as part of initial 'induction' therapy with other DMARDs but are tapered as rapidly as clinically feasible (49). This approach confers additional structural protection when compared with DMARDs in monotherapy and gives a rapid symptomatic relief (123). Intra articular injections of GC are also part of the treat-to-target protocol.

Aminopterin, an anti-folate drug, was first used in 1951 in RA patients and rapid improvement of sign and symptoms occurred (124). The drug was later modified to offer easier synthesis and called methotrexate (MTX). At this time the rheumatology community seemed uninterested due to enthusiasm for GC and concerns over toxicity. Two placebo controlled trials were done in the early 1980s and based on these the drug was approved for use in RA in 1988. MTX is now the anchor drug in the treatment of RA, both in monotherapy and combination therapy (49). There is convincing evidence that MTX in combination with low-dose GC is the optimal approach when treating patients with early RA (70,125). In the BeSt study this combination was compared to MTX in combination with an anti-TNF drug, and in the tREACH and CareRA study

MTX and GC where compared to combinations of csDMARDs and GC (94,126,127). There was no difference in outcomes in these trials and more favourable short-term safety profile than when used in combination with other csDMARDs. MTX also optimizes the effect of some bDMARDs and improves treatment continuation (128,129).

Other csDMARDs with proven modifying effect on radiographic progression include sulfasalazine and leflunomide. These are used in combination with MTX if MTX alone provides inadequate response or in monotherapy if MTX is contraindicated or not tolerated (49). Hydroxychloroquine is often used in combination with other csDMARDs but the disease modifying effect is minimal. The combination of csDMARDs after inadequate response to MTX is controversial and in the recent EULAR guidelines only recommended in the absence of unfavourable prognostic factors (49). Otherwise the addition of a biologic DMARD is recommended.

Biologic DMARDs

Biologic therapy refers to the use of medications that have been developed to target a specific molecule and/or pathway. These are widely available for the use in RA and currently have four different modes of action (130). Inhibition of TNF (anti-TNF), interleukin 6 receptor inhibition (tocilizumab), T-cell co stimulation blockade (abatacept, ABT), and B-cell depletion (rituximab). There are five different anti-TNF compounds available, four anti-TNF antibodies (infliximab, IFX; adalimumab, ADA; certolizumab-pegol, CZP and golimumab) and one recombinant TNF receptor fused to a human Fc molecule creating a bivalent TNF binding agent (etanercept, ETN).

IFX defined the fundamental importance of TNF in the pathogenesis of RA in the early 1990s (131). It is the only anti-TNF treatment given as an intravenous infusion. Along with ETN, IFX was the first biologic treatment available for the treatment of RA in Sweden in 1999 (132,133). ADA has been available since 2004 and RTX was shown to be effective in RA in the same year (134,135). The other biologic treatments have been available from around 2009. Anakinra, an IL-1 inhibitor has also been available since the early 2000s, it is less effective than the other biologics and with so many other treatments available it is rarely used in RA (130,136).

All the bDMARDs have proven their efficacy in combination with csDMARDs, the combination is generally more effective than csDMARDs alone and generally more effective than bDMARDs in monotherapy (130). No biological DMARD used as monotherapy has shown consistent statistically significant clinical or functional superiority compared with MTX (70,125). All the bDMARDs seem to have similar frequency of good outcomes in clinical trials, for example when measured with ACR20%, ACR50% or ACR70% improvement, the percentage of responders is usually 60, 40 and 20 respectively. Because of this the bDMARDs are considered equally effective, at least when combined with csDMARDs. To date there are only few

randomized controlled trials (RCT) powered to compare bDMARDs 'head-to-head'. The AMPLE study is a non-inferiority study comparing the addition of ADA or ABT to patients that only respond partially to MTX (137). The ADACTA study compared TCZ and ADA in monotherapy patients where MTX was not tolerated or contraindicated, this superiority study showed that when treated with TCZ patients were more likely to show improvement in disease activity at 6 months when measured by CDAI (138). The ORBIT trial was an open-label RCT where RTX was shown to be non-inferior to anti-TNF treatment (139). The view that bDMARDs are equally effective is mostly based on indirect comparisons and therefore the prioritization of bDMARDs is based on local guidelines, traditions and cost (130,136,140,141).

Comparison between different TNF inhibitors

The EXXELERATE study is another 'head-to-head' RCT involving bDMARDs, and the only one comparing two anti-TNF antibodies (142). Patients with active disease despite previous MTX use and with unfavourable prognostic factors were randomized to ADA or CZP, both in combination with MTX. The study was designed to show CZP superiority but no difference was noted either short term or long term (2 years) in efficacy. In addition there was no difference in safety. Patients with an inadequate response to the first anti-TNF at 12 weeks were switched to the other anti-TNF; and 60% of these primary non-responder population became responders by week 24. This suggest that different anti-TNF therapies might have efficacy in one patient but not in another.

There are some meta-analysis and systematic reviews of RCT on anti-TNF in RA (136). One from 2008 combined relative risks (RR), number needed to treat and number needed to harm from 13 trials in order to compare ADA, IFX and ETN (143). The RR for achieving ACR50 was 2.6 for ADA and ETN but 2.1 for IFX. The RR for withdrawal due to adverse event was 0.70, 1.42 and 2.04 for ETN, ADA and IFX respectively. In a systematic review from 2006 the efficacy data from 26 controlled trials was used to do an adjusted indirect comparison of ADA, ETN, IFX and RTX (144). In another systematic review from 2007 the efficacy of ADA, ETN, and IFX were compared in patients with established RA taking concomitant MTX by calculating the number needed to treat (145). The focus was on ACR50 response after at least 12 months of follow-up in double-blinded RCTs, 3 trials were included in the review. The fully adjusted number needed to treat for ADA and ETN was 4, for IFX in the standard dose of 3mg/kg every 8 weeks and the number needed to treat was 8, in patients receiving 3mg/kg every 4 weeks that number was 4. A Cochrane review from 2009 compared all available biologic agents (136). Using similar methods this review found that the number needed to treat to reach ACR50 was 5, 4, and 3 for IFX, ADA, and ETN respectively.

There are several observational studies comparing drug survival of different anti-TNF compounds. The ARTIS study group compared ADA, ETN, and IFX drug survival

over up to 5 years of follow-up adjusting for several baseline factors (146). Discontinuation rates were higher for IFX compared to both ADA (HR 1.63), and ETN (HR 1.26) and for ADA compared to ETN (HR 1.28). Similar results have been seen from several observational studies. The difference in drug discontinuation between compounds is usually explained by adverse events, not clinical efficacy (147–150). Contrasting results came from the CORRONA registry where discontinuation was more likely in biologically naïve patients receiving ADA (OR 1.42) or ETN (OR 1.27) compared to IFX (151). When examining time to drug discontinuation or dose/frequency escalation a different pattern was noted. Relative to IFX the HR for discontinuation/dose escalation for ETN was 0.77 and 1.11 for ADA. The median dose of IFX, exclusive of the loading protocol was 5.5mg/kg every 8 weeks almost twice the recommended starting dose.

The effectiveness of different anti-TNF compounds has been studied in few observational studies, both response and remission rates. The study from the CORRONA registry mentioned above compared several different response rates at 6 and 12 months in biologically naïve patients (151). Compared to IFX the adjusted odds of reaching ACR50 at 12 months were 0.72 for ADA and 1.03 for ETN. The adjusted odds of reaching CDAI remission at 12 months after treatment start was 0.69 and 1.15 in ADA and ETN respectively compared to IFX and the odds of being in DAS28 remission at 12 months was 0.89 and 1.01 for ADA and ETN, respectively, compared to IFX. As mentioned above the patients on IFX had almost twice the recommended starting dose in this study while ADA and ETN were treated with the recommended dose of 40mg every 2 weeks and 50mg/week, respectively. When dose escalation was imputed as non-response the odds of reaching DAS28 remission at 12 month were 1.22 and 1.57 for ADA and ETN compared to IFX.

In a nationwide study from the DANBIO registry several outcomes including DAS28 and CDAI remission were compared at 6 and 12 months after start of ADA, ETN or IFX in biologically naïve patients (148). Compared to IFX the odds of reaching any positive outcome at 6 or 12 months were higher for ADA than IFX including DAS28 and CDAI remission. (OR 1.78 and 1.83 at 6 months respectively). Compared to ETN the odds of reaching DAS28 or CDAI remission were higher for patients receiving ADA (OR 1.36 and 1.58 at 6 months, respectively).

In another observational nationwide study from the *Hellenic Registry of Biologic Therapies* several outcomes were compared at 6 and 12 months after start with anti-TNF (147). To compensate for drug discontinuation LUNDEX-corrected responses were calculated (152). At 12 months 17%, 15%, and 12% of patients treated with ADA, ETN, and IFX were in DAS28 remission ($p < 0.05$ for the comparison between IFX and ADA groups) and 11%, 5.1%, and 6.1% were in CDAI remission ($p < 0.05$ for the comparison between IFX and ADA groups, and ADA and ETN groups).

In conclusion, data from one RCT, systematic reviews and meta-analyses, and observational studies do not indicate a clinically significant difference between anti-TNF compounds, if any such differences might be adjusted by dose escalation.

Targeted synthetic DMARDs

Like the biologics the tsDMARDs are developed to target a specific molecule or pathway. Unlike the biologics these are small molecules. The first tsDMARD was tofacitinib, an oral, small-molecule Janus kinase (JAK) inhibitor (70). In contrast to most available bDMARDs tofacitinib was clinically superior to MTX in monotherapy with almost 40% of patients improved according to the ACR70 response at 6 months (153). Baricitinib, another JAK inhibitor appears to have a similar efficacy as tofacitinib and the bDMARDs (130). In a 'head-to-head' study baricitinib showed superior clinical and functional effect when combined with MTX in comparison to ADA (154).

These tsDMARD are recommended only after failure to meet the treatment goal with MTX and in the presence of unfavourable factors (49). Because of the long-term experience the current practice is to start with bDMARDs in this setting and only to start tsDMARDs after failing more than one bDMARD.

Aim of the thesis

The overall aim of the thesis is to examine different aspects of remission in RA patients with a particular focus on sustained remission (SR).

More specifically the aims were to study

In the SSATG population, patients with established RA in daily clinical practice *(Paper I and Paper II)*:

- the frequency, possible baseline predictors, timing and duration of SR
- the difference between anti-TNF medications used as first biological treatment with regard to frequency, duration and timing of SR
- the possible beneficial effect of SR compared to occasionally reaching remission regarding physical function as measured by HAQ
- different types of remission criteria and their possible effect on SR

In the SRQ population, patients with RA in daily clinical practice *(Paper III and IV):*

- the prevalence of SR during the first ten years after symptom onset and the possible difference in prevalence of SR between patients with early and established RA
- the timing of onset of SR and duration of SR
- the possible baseline predictors of SR in patients with early and established RA
- secular trends in remission and SR in RA i.e. whether proportion of patients reaching SR and the time to SR have changed over time

Study population and methods

The SSATG database

Paper I and II

All patients included in these studies were monitored according to a standardised clinical protocol of the South Swedish Arthritis Treatment Group (SSATG) (133,155). The protocol was developed in 1999 at the Department of Rheumatology in Lund but was soon expanded to involve other Rheumatology units in the region and covered a population of about 1.3 million inhabitants (Figure 8). The design was modified from previous nationwide protocols for early RA monitoring to be more suitable for monitoring of biologic treatments. The aim was to be able to detect outcomes unavailable within RCTs such as uncommon adverse events and to study the efficacy of biologic treatment through large-scale longitudinal data collection in routine clinical care. Therefore variables important for drug monitoring including registration of adverse events and reasons for treatment termination were registered systematically. Data entries were completed manually from paper forms received from each unit, this ensured uniform registration and minimized errors. The treating physician also received feedback in case of incomplete data ensuring complete data, as well as a graphical overview of efficacy data (Appendix D). Several validation studies have proved it to be population-based for patients with RA with coverage of pharmacy sales of > 90% (156,157). In Sweden the government is the only buyer of healthcare and during the study period the treating physician had no restrictions for selecting biologic therapy nor had to taper treatment during remission. The diagnosis of RA was based on the judgement of the treating physician, a systematic review of the case records of a sample of RA patients demonstrated that 98% fulfilled the 1987 ACR classification criteria (133). Each treatment was registered separately, meaning that each patient could be registered several times.

According to the SSATG protocol, at the start of biologic therapy, information regarding disease and earlier/concomitant treatment were reported by the treating physician (Appendix A). All patients were evaluated at 3, 6, and 12 months (optionally 0.5, 1.5 and 9 months) an thereafter at least once a year. Clinical monitoring included TJC and SJC (28 joint count), PtGA, VAS pain, HAQ, EGA, European Quality of Life-5 Dimensions (EQ-5D) as well as registration of actual dose of concomitant

DMARDs, GCs and NSAIDs (yes/no) (Appendix C). ESR and CRP were also registered at each visit. Since the registry was organized around treatments, patients were no longer monitored in the registry if therapy was terminated, but the reason for treatment termination was registered (failure, toxicity etc.). All adverse events were prospectively collected by the treating physicians. Patients were independently urged to report adverse event by specials forms distributed at each visit. In Sweden EGA has traditionally consisted of applying one of five disease states, remission, low, mild, high, maximum, rather than a continuous VAS scale. In the SSATG database this has been converted to: nil, 25, 50, 75 and 100 respectively to calculate SDAI and CDAI scores.

The main strength of SSATG is good coverage and accuracy of data with relatively little data missing. From the population included in papers I and II only 1% of patients in SR were lost to follow-up and when in SR on average 2.4 DAS28 scores were completed each year. After 2012 SSATG is merged into the national quality register SRQ.

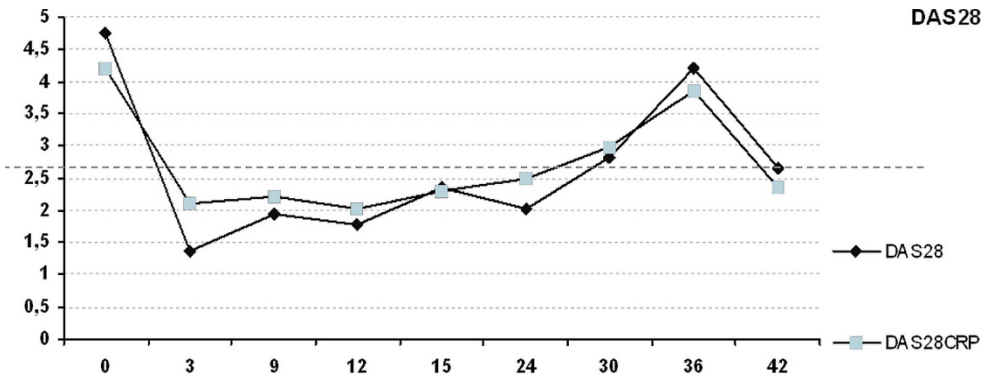


Figure 6. Screenshot from the SSATG database showing disease activity (DAS28 ESR and CRP)
Time in months is shown on the x axis. This patient reached remission after 3 months of treatment but escaped after 30 months, so the remission was sustained for 27 monts.

SRQ

Paper III and IV

The SRQ is originally a national register for follow-up of incident RA that has over time expanded to cover other rheumatic diseases. It was started in 1995 by the Swedish Society for Rheumatology and incorporates earlier registries as the Early Arthritis Register (including TIRA and BARFOT) and later incorporated biologic registries (ARTIS including SSATG and STURE) (24,133,158–160). Since 2012 SRQ is a national registry with cooperation of 56 rheumatology units from every region in Sweden (161). The earlier registries were then conjoined and focus has been on high coverage of all arthritis patients from disease onset. The completeness is about 83% of

all patients diagnosed with RA in Sweden and it covers 87-95% of all patients treated with biologics (162,163). The first patients were included in the early arthritis registries in 1992 but patients included in the biologic registries from 1999 were often included several years after disease onset and no disease activity data are available prior to inclusion.

At inclusion into SRQ, data on symptom onset, date of diagnosis and all previous anti-rheumatic treatments (DMARDs, glucocorticoids, NSAIDs or biologics) are collected by the treating rheumatologist. Operated as part of routine care, at each follow up visit information on number of swollen (SJC) - and tender joints (TJC), evaluator global assessments of disease activity (EGA, 0-100), and markers of inflammation (CRP/ESR) are registered by the physician (Appendix F). In addition, data on changes in anti-rheumatic treatment and in case of discontinuation the reason for discontinuation is collected. The calculation of patient related outcomes - HAQ and EQ-5D (using the United Kingdom Time Trade-Off based preference set) are based on patient's answers to questions regarding health and function which are registered at each follow up visit and include; PtGA, VAS pain (164). Disease duration was originally registered as the time from diagnosis, but in later years both estimated date of symptom onset and date of diagnosis is registered. Where available we have calculated symptom duration as from the date of symptom onset. In this thesis we call it symptom duration, but when referring to previous decades it would be more accurate to call it disease duration.

Physicians benefit from participation since access to the registry provides a powerful tool to aid in decision making. All previous and current DMARD treatment can be visualised on a timeline including disease activity, physical function and pain (Appendix F). Participation benefits patients by being involved in their own care which leads to higher participation rates and increases the quality of the data obtained.

The SRQ is a powerful research database, it includes large number of patients over extended periods of time but unlike the SSATG workflow, there is no systematic feedback when data is missing increasing the risk of missing data.

Study population

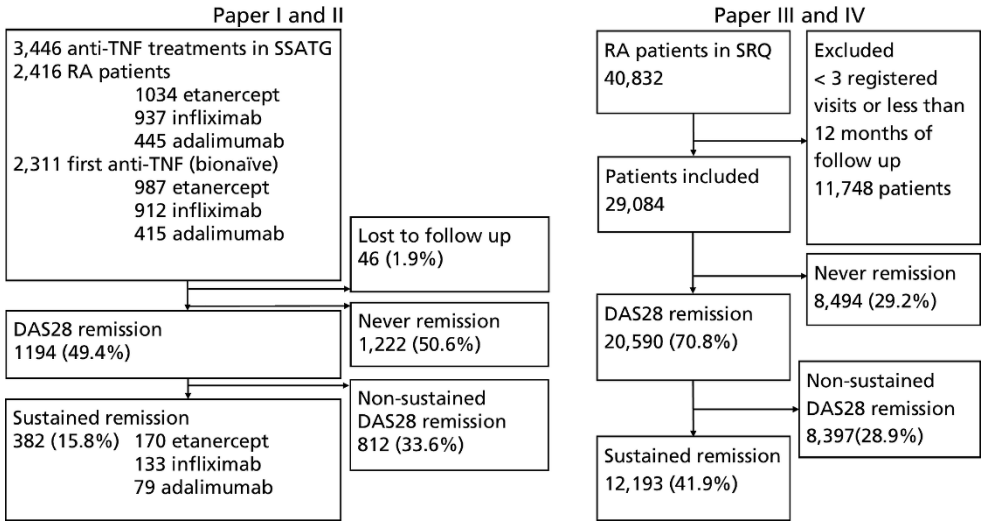


Figure 7. Study population
A total of 3,446 treatments were registered in 2,416 RA patients during the period of which 2,311 where first anti-TNF treatment. Fourty six patients were lost to follow-op.
40,832 patients with RA were registered in the SRQ over the study period. Patients with short follow up or no registered visits were excluded.

Paper I and II

All adult patients with RA registered in the SSATG database and starting treatment with ADA, ETN or IFX, during the period from March 1999 through December 2009 were included. Follow up data were collected through June 2010 or treatment termination/switch to another biologic. No formal level of disease activity was required; however, the patients should have received at least one DMARD previously without acceptable response or tolerability. A total of 3,446 treatments were registered in 2,416 RA patients (Figure 7). A large proportion of this population were patients with long standing, established RA and the mean HAQ was high. ACPA and RF status was not systematically collected, neither were radiographic data. When comparing anti-TNF treatments only bio-naïve patients were analysed.

The registry was searched for individual treatments fulfilling DAS28 remission criteria (<2.6) at any point. One researcher (JTE) scrutinized every treatment case by case evaluation whether patients were in sustained (at least two consecutive visits, duration of at least 6 months) or non-sustained remission (NSR) (Figure 6). Patients were categorized as in SR, NSR or never remission. Only the first SR was analysed, i.e. each patient could only contribute with one SR. To compensate for intercurrent diseases

(such as infections) patients were allowed to have DAS28>2.6 on one occasion given that they fulfilled the remission criteria for at least 6 months before and afterwards.

Similarly, the registry was searched for individual treatments fulfilling the SDAI, and CDAI criteria (≤3.3 and ≤2.8 respectively) and those in SR, separating those with NSR and never remission.

ADA was administered as a 40 mg subcutaneous dose every other week. ETN was administered once or twice a week with 50 mg or 25 mg subcutaneously, respectively. IFX was infused at 3mg/kg at 0, 2, 6, and then every 8th week. The dose of IFX could be increased in case of lack of efficacy. Through 2006 the average dosage after 6 months of IFX treatment was about 5mg/kg every 8th week (165).

Table 5. Some demographic characteristics of the patient populations

	Paper I and II	Paper III and IV
Setting	Regional bioregistry (SSATG)	National RA registry (SRQ)
Number of patients	2,416	29,084
Mean age (years)	56.0	58.1
Mean (median) disease duration in years	11.8 (8.8)	7.5 (1.9)
Female sex (%)	77.0	72.3
Patients that reach DAS28 SR	382	12,193

Figure 8. The geographical uptake area in SRQ and SSATG

Paper III and IV

Patients eligible for these studies were adults with a diagnosis of RA according to the clinical judgment of the treating physician, registered in the SRQ registry through December 2012. The first patients were included in the early arthritis registries in 1992 but patients included in the biologic registries from 1999 were often included several years after disease onset. That means that the span of disease onset reaches back to the 1930s, with very limited follow-up data available (previous DMARDs are registered) before inclusion in the registry.

A total of 40,832 RA patients were registered during the study period. Some of these had no registered visits and a few were under the age of 18 and were excluded. To be able to calculate SR patients with less than three registered visits were excluded as well as patients with less than 12 months of follow-up. That left us with 29,084 adult RA patients (Figure 1). Of these roughly 50% had all data available for classification

according to the 1987 ACR criteria, 95% fulfilled these criteria. ACPA status was available in 5,640 patients and 73.2% of those were ACPA positive.

Almost one in four (6,551 patients) were included in the registry within 6 months from symptom onset, these were categorized as early RA patients while others were categorized as having established RA. The median time from symptom onset to registration in SRQ is two years and ranging up to 78 years. Because of this skewness, baseline data for patients included in the registry after the median time of two years were excluded for parts of the analysis. Table 5 summarises some key numbers from each cohort.

Statistical calculations

Descriptive statistical methods were used to describe baseline demographic and clinical characteristics. Kruskal–Wallis one-way analysis of variance and Mann–Whitney *U* test were applied to analyse variance between groups in continuous variables, whereas Chi-square test (2-distribution) was used for comparison between categorical variables. Correlations were calculated using Spearman correlation test. Additional statistical calculations were performed in the different papers as follows.

Paper I

Response rates for different drugs were calculated using per-protocol, intention-to-treat (estimated fraction of starters still in the study at time T divided by starters) and LUNDEX correction (LUND Efficacy indeX). LUNDEX = (Fraction of starters still in the study at time T) x (Fraction responding (in SR) at time T) (152). The different methods were chosen to account for missing follow-up data since different drugs can have different drug survival or adherence.

Paper II

Mean HAQ was calculated for each patient at each year and for patients in SR and NSR the mean HAQ was calculated each year after achieving remission. For statistical comparison we calculated the change in HAQ (ΔHAQ) from remission start at each year.

Paper III

Kaplan-Meier survival curves were used to estimate the time to and in SR and different groups were compared using the Holm–Šidák method.

Paper IV

The crude fraction ever reaching DAS28 remission or SR inclusion in SRQ was calculated using patients with symptom onset from 1955 to 2012. The odds of reaching SR for each decade were estimated using binary logistic regression. According to year of symptom onset the estimated fraction to have reached SR at each time point during the first 5 years after symptom onset were estimated using Kaplan-Meier estimates (1-survival). In order to address the problem of multiplicity and Type I error, Holm–Šidák method was used to statistically compare different years (166).

Table 6 summarises the main statistical methods used in the different papers.

Table 6 Statistical methods used in Paper I-IV

	Comparison	Assessment period	Statistical methods
Paper I SSATG	Predictors of SR Time to and in SR Comparison between ADA, ETN and IFX	1999-2009	Binary logistic regression Kaplan-Meier estimator Cox-proportional hazard models LUNDEX correction
Paper II SSATG	Comparison between NSR with SR Comparison between DAS28, SDAI and CDAI	1999-2009	Confidence interval of the mean
Paper III SRQ	Comparison between early and established RA Predictors of SR Prevalence of SR Comparison between DAS28, CDAI, SDAI, ACR/EULAR	1992-2014	Kaplan-Meier estimator Holm–Šidák method Cox-proportional hazard modell
Paper IV SRQ	Comparison between odds of SR for different decades Compatison between freqency of and time to SR in different calender years of symptom onset	1992-2014	Kaplan-Meier estimator Holm–Šidák method Binary logistic regression

Ethics

The SSATG protocol quality control meets the legislative documentation required in Sweden. Therefore no formal ethical approval was required for individual analysis conducted within the registry. After scrutinizing this approach the regional ethics committee in Lund has confirmed this on two separate occasions.

Ethical approval for the studies on SRQ (Paper III and IV) were approved by the Regional ethical committee in Lund (Dnr 2014/754). The use of date from the SRQ was approved and supplied by the Register Council of SRQ (Registerrådet).

Results and discussion

Sustained remission in RA patients

Frequencies of sustained remission

Of a total of 29,084 patients with RA registered in SRQ, 20,590 (70.8%) had a registered visit with DAS28<2.6 at any time point during follow up. Almost one in three has never been in remission. However, only 41.9% experienced SR.

In anti-TNF treated patients with established RA who were monitored in SSATG, 49.4% patients had a visit with DAS28 <2.6 but only 15.8% reached SR.

The significant differences in remission frequencies between patients in SRQ and SSATG registry can probably be explained by the different populations. The SSATG cohort *(Paper I)* had an established RA and received anti-TNF treatment within the first 10 years after these being approved for use in Sweden. There was a selection towards treating patients non-responsive to sDMARDs. Many of these patients received biological treatment late in the course of their disease and had already developed irreversible structural damage and decreased physical function. These patients had higher PtGA scores. Consequently, reaching low disease activity was a more realistic goal than remission in this population. The SRQ *(Paper III)* covers a wider time span but patients have shorter disease duration at inclusion. Half of all patients have less than two years from symptom onset to inclusion and 22.5% had early RA compared to 0.4% in SSATG. This does not necessarily mean that patients in SRQ had better treatment, but that we are studying them earlier in the disease course and there is no patient selection towards non-responders.

Comparison between different remission criteria

Table 7 shows the frequencies of SR according to different remission criteria. RA patients included in SSATG showed lower frequency of SR regardless of remission criteria used.

Table 7. Frequencies of SR according to different remission critera

Remission criteria	All RA patients (SRQ, paper III)			Anti-TNF treated (SSATG,papers I,II)		
	Frequency of SR	Median SR duration (years)	Median time to SR* (years)	Frequency of SR	Median SR duration (years)	Median time to SR (years)
DAS28	41.9%	7.2	1.9	15.8%	5.25	0.7
SDAI	21.3%	4.0	2.4	7.7%	2.7	0.5
CDAI	22.2%	4.0	2.4	7.3%	2.7	0.5
ACR/EULAR	17.5%	3.5	2.5	-	-	-
*For this analysis we only used patients included within two years from symptom onset.						

The ACR/EULAR criteria are the most stringent criteria, closely followed by SDAI and CDAI. Very few patients can ever experience SDAI or CDAI criteria but not DAS28 and the overlap between SDAI and CDAI is almost complete. DAS28 is the least stringent with about twice as many ever experiencing DAS28 SR compared to the other criteria (Figure 9). This is as expected, DAS28 has consistently been shown to be the least stringent of the four.

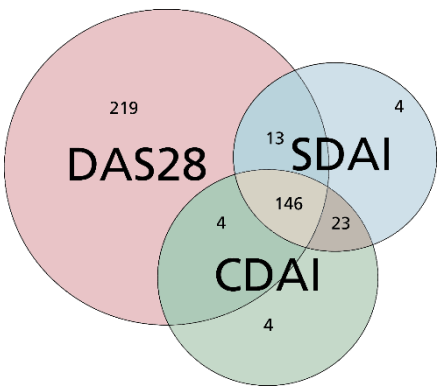


Figure 9. Vonn diagram
This diagram shows the number of patients that reached SR according to different DAI in the SSATG and how the different criteria overlap. ACR/EULAR was not calculated in the SSATG cohort.

Prevalence of sustained remission during follow up

The prevalence of SR increased during the first five years after symptom onset although the increase was only minor after the first three years. After that the prevalence was relatively stable for up to ten years. The prevalence of SR is higher in patients with early RA than in established RA, the difference already apparent one year after symptom onset (Figure 10). After about 3 years the prevalence of SR is rather stable indicating the difficulties to reach an additional improvement after what might be called a 'window of opportunity'(102,167). Most patients that experience SR do so early in the

course of the disease which confirms the importance of early initiation of active treatment and 'treat to target' strategy (114).

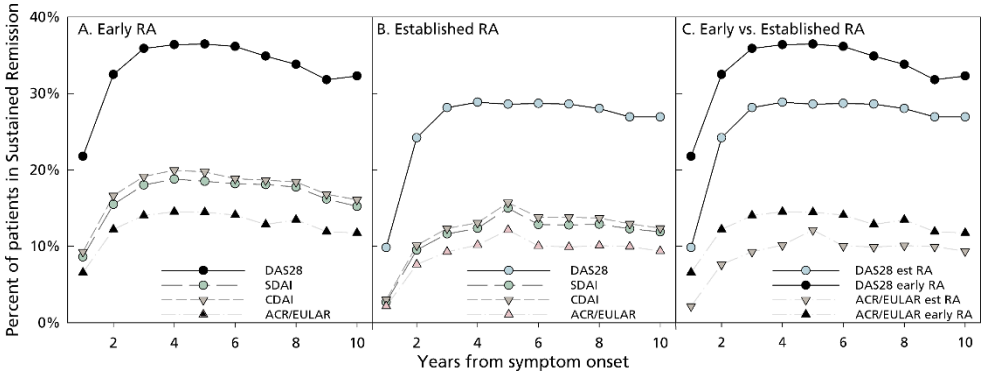


Figure 10. The percentage of patients in SRQ in SR each year after symptom onset
The lines represent different remission critera: A) Patients with early RA, B) Patients with established RA, C) Both early and established (est) RA patiens drawn according to DAS28 and ACR/EULAR SR criteria.

Time to sustained remission

Table 7 shows the median time from symptom onset to SR in the two cohorts and for different remission criteria. Compared to the SRQ cohort, the median time to SR in the SSATG cohort was shorter regardless of remission criteria used.

This difference might be explained in part with the fact that not all follow up data is available from SRQ patients. Many were included in the SRQ registry after treatment start, whereas baseline and clinical data were mandatory at inclusion in the SSATG at treatment start. This implies that we miss all those that reach SR before inclusion in the SRQ. To minimise this loss we only analysed patients included within two years from symptom onset.

For statistical comparison we estimated the median time to SR in RA patients in SRQ. The median time to DAS28 SR was significantly shorter than CDAI, SDAI and ACR SR. Median time to CDAI/SDAI SR was significantly shorter than to ACR SR (log-rank test $p<0.001$ for all comparisons except SDAI vs CDAI $p=0.026$).

The median time (SD) to DAS28 SR was 1.4 (3.3) years in early RA compared to 2.3 (3.3) years in established RA. The timing of SR is illustrated in a histogram (Figure 11). Although most patients do reach SR early on in disease, still a few patients require 15 years from symptom onset to reach their first SR (SRQ) (Figure 11).

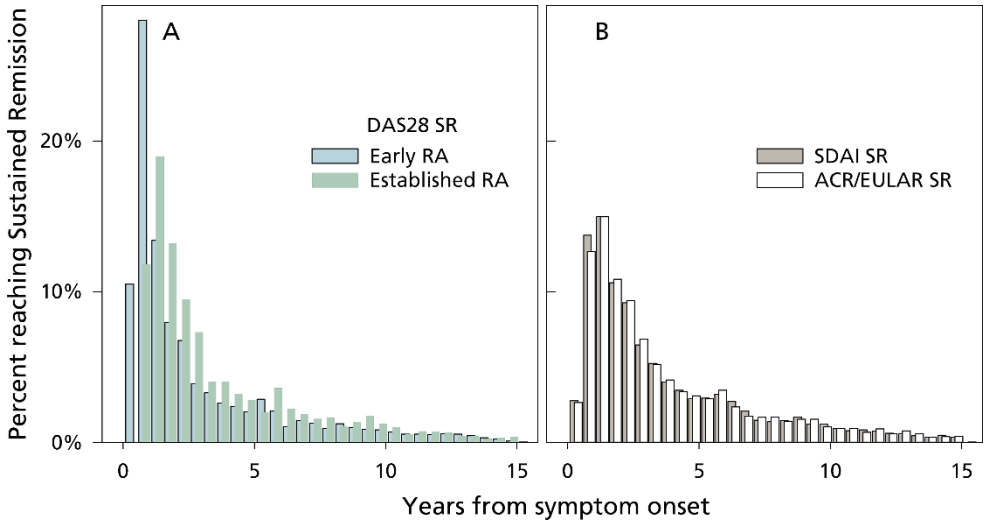
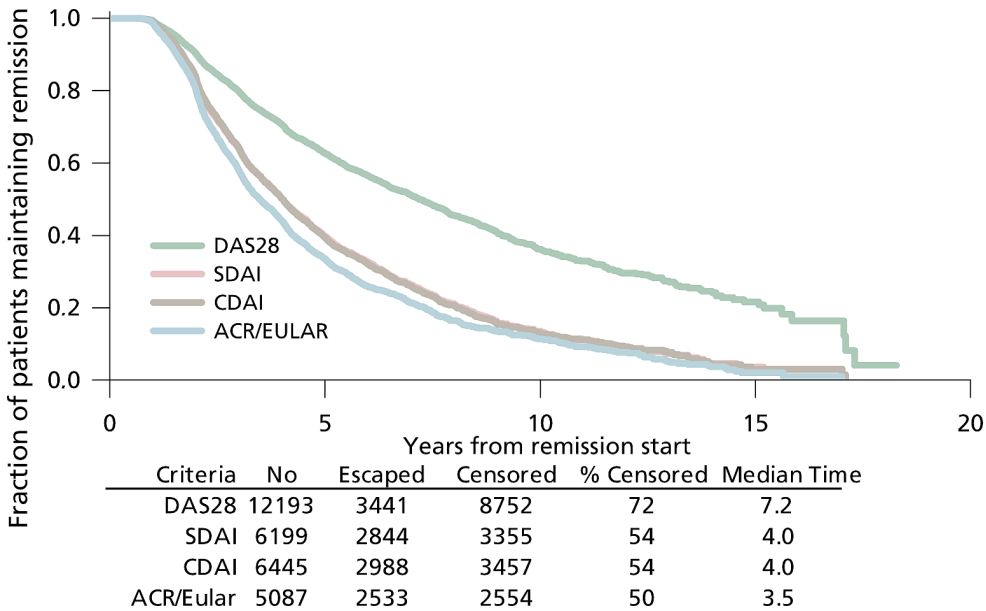


Figure 11. Modified Histogram showing the timing of reaching SR in SRQ
The bars represent the percentage of patients that reach SR at each time point during the first 15 years after symptom onset. CDAI SR is not shown since the histogram is almost identical to SDAI SR. For this analysis patients with more than two years from symptom onset to inclusion in the SRQ were excluded.

Time in sustained remission

The percentage of SSATG patients remaining in SR at 12, 24, and 48 months were 91.3%, 74.8% and 60.0%, respectively. The median estimated duration of DAS28 SR was 5.3 years in SSATG and 7.2 (ranging up to 18.3) years in SRQ. In both cohorts many were still in SR at the end of the follow-up period. CDAI and SDAI remission times are almost identical but patients stay longer in DAS28 remission ($p<0.001$) and shorter in ACR remission ($p<0.001$) (Figure 12). Of the 189 patients that escaped from SR in the SSATG cohort; 159 continued on the same anti-TNF treatment.



Criteria	No	Escaped	Censored	% Censored	Median Time
DAS28	12193	3441	8752	72	7.2
SDAI	6199	2844	3355	54	4.0
CDAI	6445	2988	3457	54	4.0
ACR/Eular	5087	2533	2554	50	3.5

Figure 12. SRQ data. Kaplan-Meier curve showing the estimated time in SR according to the different DAI
Remission time is defined as time from first visit in SR to subsequent visit with higher disease activity (escape). Patients still in remission at last visit are censored, therefore remission times are possibly underestimated. CDAI and SDAI remission times are almost identical and the SDAI curve is hidden behind the CDAI curve.

The fact that there are so many patients that experience NSR or occasional remission but not SR indicates that the risk for escape after first visit in remission is high. After the second visit in remission patients are more likely to stay in remission, in fact most SR patients stayed in remission for several years. It is common practise in Sweden to change the visit frequency from every 3 months to every 12 months once in remission. Our results support the suggestion that visit frequency should only be changed when the treatment target is sustained over time (50).

In both cohorts many were still in remission at last follow up, these patients are censored from the Kaplan-Meier estimation, therefore our results of time in remission are possibly somewhat underestimated in both cohorts. The difference between cohorts is small and might be due to longer available follow up time in the SRQ cohort. We have not studied what happens after patients escape from remission and we only analyse the first SR episode. As mentioned, most patients in the SSATG were not switched to another bio treatment after escape. This indicates that patients go from remission to low disease activity and possibly to SR again. Time in remission is affected by the visit frequency, but this effect evens out in both ends of the remission period. When the time between visits in SR exceeded two years we considered patients to have escaped from SR.

There were particularly five remission patterns observed in the SSATG registry. Most common was the early escape with less than six months in remission. But for patients in SR we observed a) early sustained remission, b) steady decline in disease activity with late sustained remission, c) early sustained remission with escape and d) relapsing remission with patients swinging between low/medium disease activity and remission.

Predictors of sustained remission

RA patients in the SSATG cohort who were treated with concomitant MTX had higher frequencies of SR compared with patients receiving biological treatment as monotherapy. In total, 12.9% of MTX treated patients were in SR at 12 months compared to 5.4% on monotherapy. More bio-naïve patients reached SR (16%) than patients previously treated with any biologic treatment (11%) (SSATG). The use of MTX at baseline was the only clinical characteristic positively associated with SR at the start of an anti-TNF treatment (OR 1.67). HAQ and DAS28 were negatively associated with SR, the odds for SR decreased with 0.39 and 0.62 respectively with an increase in the score by 1.0. (Figure 13)

Surprisingly few patients in the SSATG received concomitant MTX, but almost all had received this treatment previously and had stopped due to non-responsiveness or intolerance.

Baseline clinical features at inclusion in the SRQ that are generally indicative of more active disease were negatively associated with SR. When all patients were included in the analysis, HAQ, ESR, VAS pain and TJC but not DAS28 predicted SR. However, among early RA patients DAS28 was negatively associated with SR. EGA was the only clinical variable positively associated with SR. Table 8 summarizes the results of the predictor analysis. Continuous variables were standardized before inclusion in the SRQ predictor analysis and are therefore not comparable to the SSATG ratios. SJC was omitted from the presented model due to high collinearity with TJC, but when a separate model was analysed switching these two variables, SJC did not predict SR. This might be explained by the fact that in DAS28 the impact of TJC is twice as high as the impact of SJC (Table 4, $0.56\times\sqrt{TJC}$ *vs* $0.28\times\sqrt{SJC}$).

Our results are in line with results reported from others (85,91,99–101). HAQ seems to be the outcome measure that has the strongest association with SR. The positive association of EGA with SR is interesting. This might reflect that when physicians consider patients to have more active disease the treatment is intensified, PtGA does not have the same effect. We have not analysed any treatment details from the SRQ.

Table 8. Predictors of SR at inclusion in the SRQ

Two separate models were done for both all patients and early RA (not shown in table). Model A) Adjusted for sex and age and Model B) Multivariate analysis. Variables included in the primary analysis; age, sex, DAS28, PtGA, pain, HAQ and ESR. Another model with DAS28 omitted and EGA and TJC included was done because of collinearity. ACPA status was available in 5640 patients and a separate model was done with ACPA included. The table shows the results of the first model including DAS28 and HAQ. Continuous variables were standardised before inclusion in the predictor analysis.

	Model A			**Model B**		
	HR (95% CI)		**p-value**	**HR (95% CI)**		**p-value**
Age (decades)				0.83	(0.82–0.84)	<0.001
Male Sex				1.51	(1.44–1.57)	<0.001
Early RA	3.18	(3.04–3.32)	<0.001	3.45	(3.29–3.62)	<0.001
DAS28 ESR	0.80	(0.78–0.81)	<0.001	0.98	(0.95–1.01)	0.190
PtGA (0-100)	0.78	(0.77–0.80)	<0.001	0.95	(0.92–0.99)	0.005
Pain (0-100)	0.79	(0.78–0.81)	<0.001	0.99	(0.96–1.00)	<0.001
HAQ (0-3)	0.68	(0.67–0.70)	<0.001	0.72	(0.70–0.74)	<0.001
ESR (mm)	0.79	(0.78–0.81)	<0.001	0.84	(0.82–0.87)	<0.001
ACPA (+)	0.86	(0.79–0.94)	0.001	0.86	(0.78–0.94)	0.001
EGA (0-100)	0.93	(0.91–0.94)	<0.001	1.16	(1.13–1.19)	<0.001
TJC (0-28)	0.87	(0.86–0.89)	<0.001	0.93	(0.90–0.95)	<0.001
SJC (0-28)	1.00	(0.98–1.01)	0.595			*
EQ-5D	1.24	(1.16–1.33)	<0.001			**

*SJC was left out of the multivariate analysis since it has a high correlation with TJC.
**EQ-5D was left out of the multivariate analysis because of high collinearity (r>0.6) with multiple variables.

Similar demographic predicted SR in both cohorts, female sex and higher age were negatively associated with SR.

Early RA, i.e. early diagnosis and the chance of early treatment, was the strongest predictor of SR in the SRQ cohort. In the SSATG disease duration did not predict SR (*Paper I*). These patients had established disease and about 12 years of disease duration, only 13 patients had less than 6 months disease duration at anti-TNF start. We tried to stratify patients according to different duration of disease but when entered into multivariate model, variables such as HAQ, indicating level of physical function, overshadowed the effect of disease duration.

This is probably the most important information from the predictor analysis. Implementing measures that increase MTX compliance and strategies that lead to early diagnosis of RA will probably result in more patients experiencing SR.

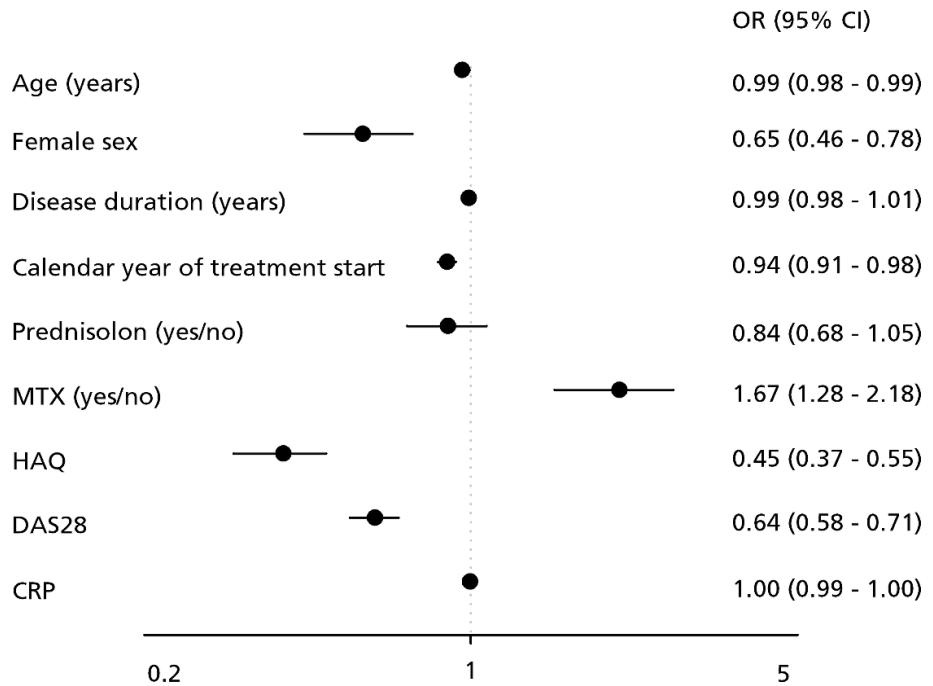


Figure 13. Predictors of SR at the start of first anti-TNF treatment.
Because of colinearity, separate models were used for DAS28 and HAQ, per unit increase, with the results from the HAQ model shown here. Female sex, male sex as a reference. DAS28 was based on the ESR level with 4 variables.

Secular trends in sustained remission

Treatment strategy in RA has changed dramatically during the last 20 years. Currently, the focus is on early diagnosis and treatment which is the reason that patients from the early 1990s differ significantly from those with symptom onset in the late 2000s. As illustrated, (Figure 14) early RA patients included between 1991 and 2000 had mean 0.32 years from symptom onset to first registered visit in the SRQ. The corresponding time was 0.30 year 2001-2010, and 0.27 years 2011-2014 (p<0.001).

Over the same time period SJC decreased from 9.5 to 9.0 to 7.6 (p<0.001) and CRP from 33.1 mg/L to 29.3 and 22.6 between 2011 and 2014 (p<0.001). Physical function is less impacted as HAQ has gone from 1.06 to 1.00 (p=0.004). At the same time there is a trend towards increased experienced pain (not shown), higher PtGA and EGA. There is only a modest decline in the disease activity score as measured by DAS28 (5.19 to 4.99 (p=0.001))

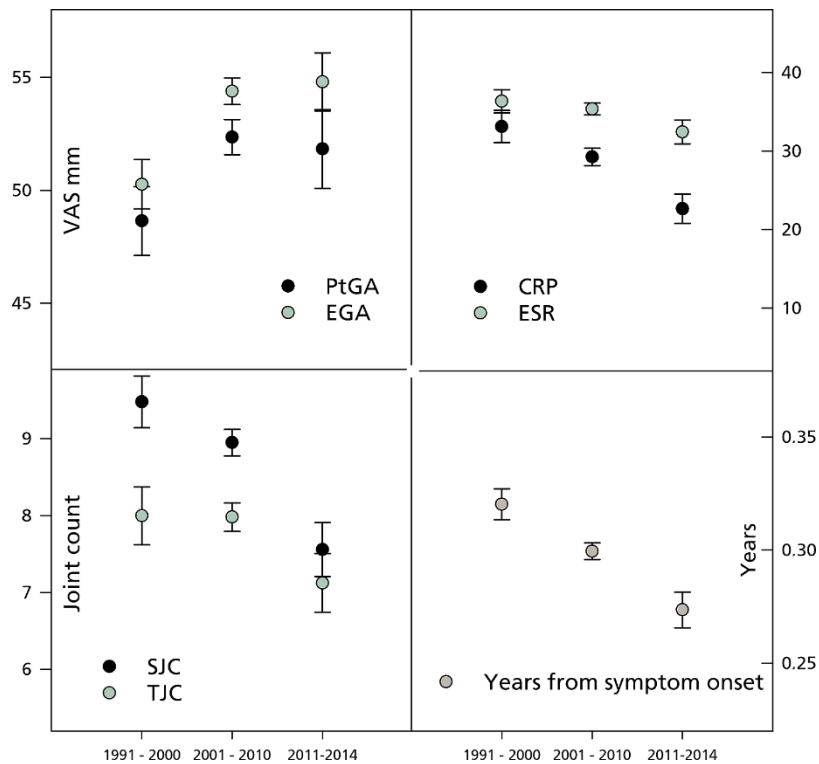


Figure 14. Secular change in clinical characteristics at baseline in the SRQ.
Patients with early RA at inclusion in the SRQ. Comparing patients with symptom onset between 1991 and 2000 with 2001-2010 and 2011-2014. Numbers are mean shown with 95% confidence interval.

Of all patients with disease onset in the 1980s, 1990s, and 2000s, 35.0%, 43.0% and 45.6% reached SR respectively at any time during follow up ($p<0.001$ for each increment). **Table 9** shows the OR of reaching SR for patients with disease onset in a certain decade compared with the decade before.

Table 9. Odds of reaching SR

This table shows the odds ratios (OR) with confidence interval (CI) of reaching DAS28 SR for patients with symptom onset in a given decade—with the previous one as a reference. The column to the right shows the OR for reaching SR within 5 years, because of lack of events we were not able to calculate this for all periods. A higher number favours the decade to the right.

Reference		Decades	All available follow up	5 years
			OR (95 % CI)	OR (95 % CI)
1980 and before	vs	1981 - 1990	1.26 (1.13–1.42)	-
1981 - 1990	vs	1991 - 2000	1.40 (1.28–1.52)	-
1991 - 2000	vs	2001 - 2010	1.11 (1.05–1.18)	3.97 (3.67-4.30)

When calculating the crude fraction of patients with disease onset in available calendar years, there is a trend towards increased incidence of both remission ever and SR towards a peak in 2006 but after that the incidence drops (Figure 15).

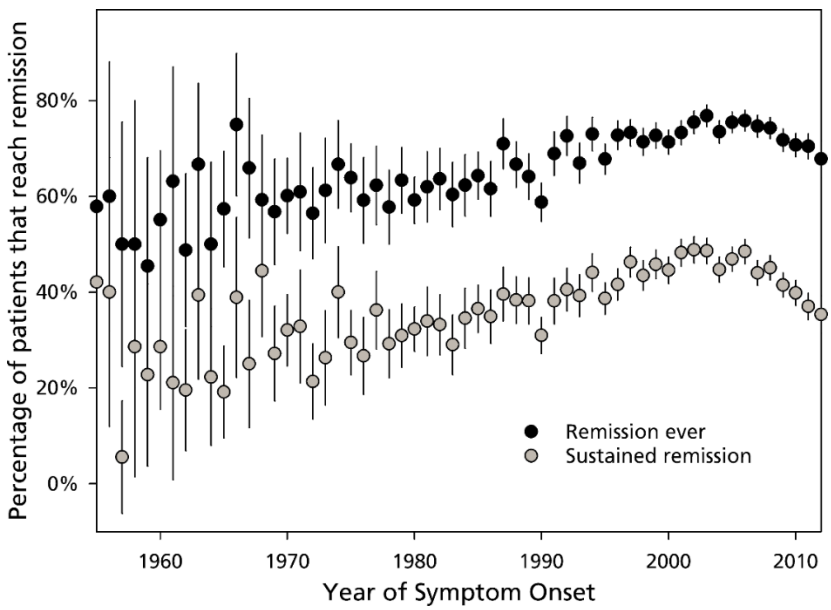


Figure 15. Incidence of DAS28 remission stratified after year of symptom onset.
The figure shows the fraction of patients, from each calendar year of symptom onset, reaching DAS28 remission ever or SR - after inclusion in the registry. The error bars represent 95% confidence interval.

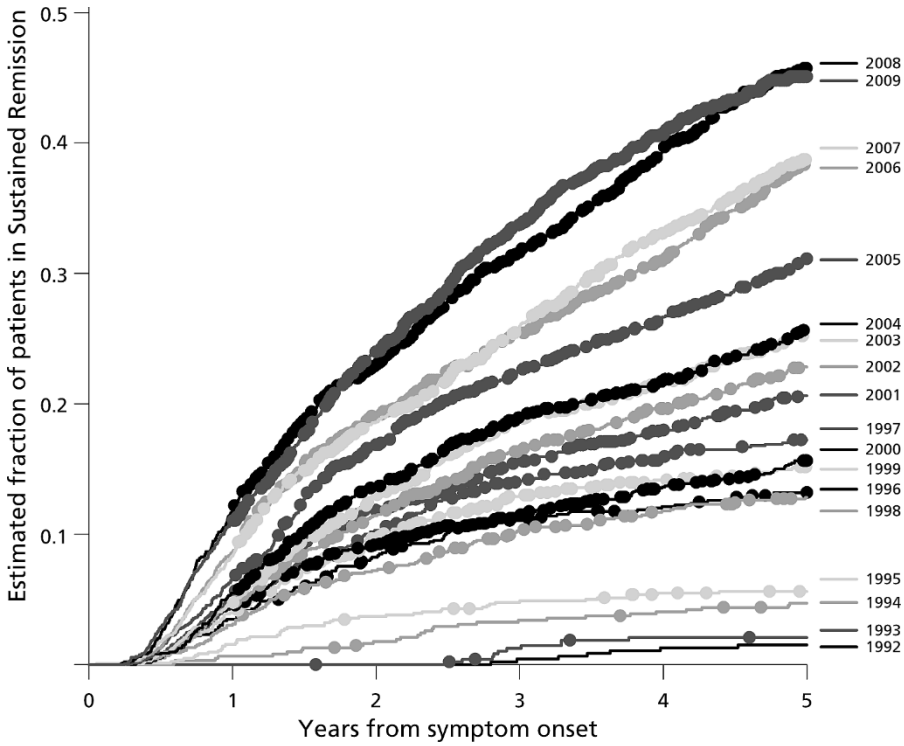


Figure 16. Fraction of patients from each year reaching SR within 5 years
A Kaplan-Meier curve showing the estimated fraction of patients that have reached DAS28-SR, at each time point after symptom onset. Stratified into years of symtom onset. No patients with symptom onset before 1992 reached SR within 5 years.

Figure 16 shows the patients reaching DAS28 SR at each time point during the first five years and after stratification into year of symptom onset. There is a significant improvement almost every other year with some exceptions.

No patients with symptom onset before 1992 reached SR within 5 years and very few of those with onset in the years after. After 1995 there is a steady increase in the frequency of SR with over 45% of patients with symptom onset in 2009 reaching SR within the first 5 years. The median time to SR changed from infinity for 1995 to under 7 years for 2006.

There seems to be a trend towards lower disease activity at diagnosis. Some have argued that RA is becoming milder in itself over time (168). Our data show a trend towards earlier diagnosis with about three months from symptom onset to diagnosis in early RA compared to four months before. Efforts have been made in Sweden and elsewhere towards earlier diagnosis, but this could nevertheless be a result of changes in the SRQ, where physicians now register symptom onset more systematically (as opposed to disease onset). Patients first develop arthralgia that then converts to clinically swollen

joints. If patients present earlier in this process then they have fewer swollen joint and somewhat lower ESR, so the decrease in these parameters might simply reflect earlier diagnosis. Despite this both PtGA and EGA, and pain increase over time, which could reflect changed expectations both among physicians and patients and increased intolerance for anything that negatively impacts physical function or quality of life. PROs may therefore not be reliable when investigating secular trends in disease activity.

There is a clear trend towards shorter time to, and increased incidence of SR. The odds of reaching SR have improved with each consecutive decade. This is most likely due to the paradigm shift in RA management with earlier diagnosis, tight control and treating patients to the target of remission (49,120). The incidence of SR is dependent on the follow up time as the absolute chance of reaching SR increased with time. This explains the dip in the figure above (Figure 15) where the fraction of patients reaching SR or remission ever peaked in 2006 and dropped after that. We did sub-analysis (not shown) with only patients included within two years and another excluding patients with less than 5 years follow up; then the line became flat after 2006. This also explains why the odds of reaching SR in the 2000s compared to the 1990s is only just over one. When including only SR during the first 5 years after symptom onset the odds are much higher.

Figure 16 illustrates the most reliable evidence for improved incidence of SR. We restricted the analysis to 5 years of follow up and analysed only the population at risk at any time point. SR did not occur in the early 1990s but there is a dramatic improvement after 1995. This improvement in patients with symptom onset in 1996-8 might be an effect of the anti-TNF treatments being available in Sweden (1999). However, initially these treatments were usually reserved for difficult to treat RA patients with long standing disease who failed other treatments. More likely the improvement is attributable to the increased use of MTX during these years.

Rather disappointingly, even though there is a dramatic improvement in the number of patients reaching SR over the period, less than half of the patients with symptom onset in 2009 have reached the least stringent SR criteria - DAS28 - within five years from symptom onset.

Physical function in sustained remission

Physical function at remission start is better in patients that reach SR than those that reach SR occasionally. But when comparing these groups over time the mean HAQ diverges and the relative difference in HAQ (ΔHAQ) continues to increase as long as the SR is maintained (Figure 17). After five years in SR the difference in HAQ has increased by 0.24. If patients in SR escape from remission the relative improvement remains. The same trend is noted with both SDAI and CDAI remission. Compared to males, female patients had a higher HAQ at remission start but showed more improvement over time. SDAI or CDAI SR do not significantly improve physical function further than DAS28 SR

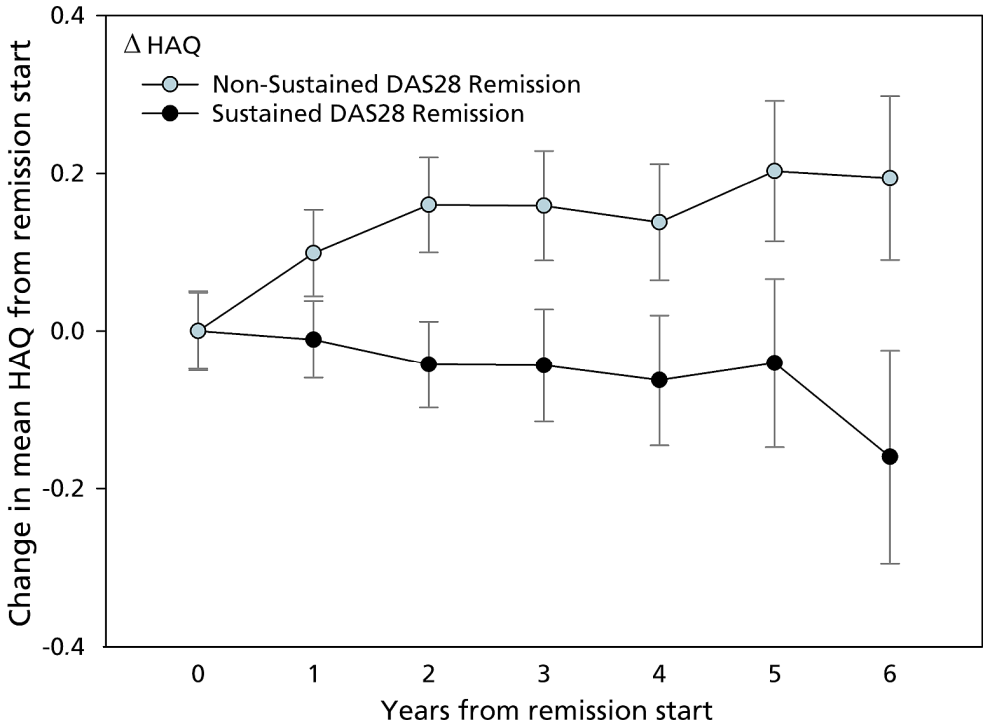


Figure 17. Change in HAQ over time in SR and NSR.
Year 0 is at start of SR or first remission for the NSR patient. After that, each point represents the mean HAQ during each year.

At DAS28 remission start 28.7% of patients had full physical function (HAQ=0) compared with 15.8% of NSR patients. After 4 years of SR 40.0% had full physical function compared with 10.4% of NSR patients, the difference being significant from the second year of remission (Figure 18).

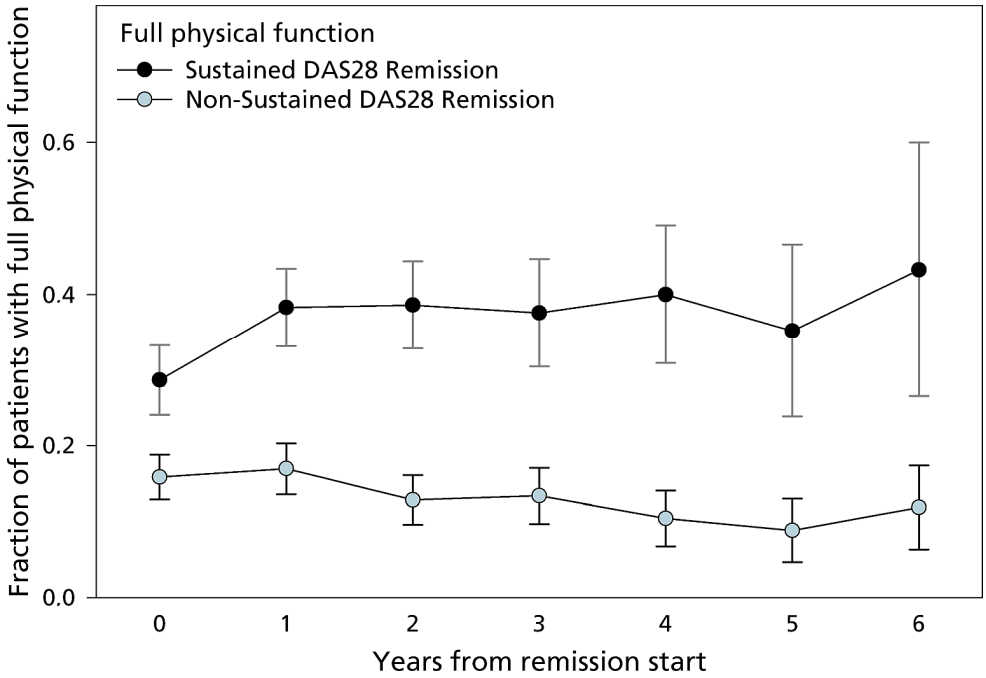


Figure 18. Full physical function (HAQ = 0).
Fraction of patients with full physical function (defined HAQ = 0) over time from remission start. The difference in fraction of patients was significant in the second year of remission ($p < 0.05$).

Compared to patients that only experience occasional remission (NSR), patients in SR develop better physical function over time, regardless of which remission criteria used *(Paper II)*. This indicates that it is not the exact state of remission but rather the sustainability of that state that is important. For the purpose of examining the benefits of SR, physical function as measured by the HAQ was chosen since it is the strongest predictor of mortality and morbidity in RA. We considered to use other variables as well and did analyse EQ-5D over time. These analysis gave the same results but we decided to publish only HAQ data. Using radiographic data would be the obvious alternative but these are not available in the SSATG.

We know from benchmarking studies in the general population that the mean HAQ begins to increase after the age of 50, particularly in females (67). Female sex had a significant impact of the difference we observed and the HAQ curves in men were flatter although showing a similar trend. Males are known to have lower DAS28 scores and more often reach remission but despite this show similar radiographic progression as females (169)(169).

This is an observational study and it is possible that the patients that continue in remission simply represent patients with the most favourable disease progression. Still the SR patients had relatively high HAQ at treatment start and several swollen joints

and long disease duration. We do not have complete information on comorbidities in our registries and were unable to adjust for factors other than RA that may influence HAQ.

When this study was published treatment guidelines focused on point remission and hinted that if physicians always aimed at remission, sustained remission would automatically follow. At the same time guidelines started to advocate for tapering of therapy once in remission. We concluded that it is the sustained state that is important and that maintaining remission should be a treatment goal.

Comparing different anti-TNF treatments

In total 17.8%, 16.4%, and 14.2% on ADA, ETN and IFX fulfilled the SR criteria *(Paper I)*. Compared to ETN and ADA, IFX patients had higher MTX dose at anti-TNF start. There were no differences in DAS28 or disease duration, but IFX treated patients had higher HAQ scores at start. More men received IFX.

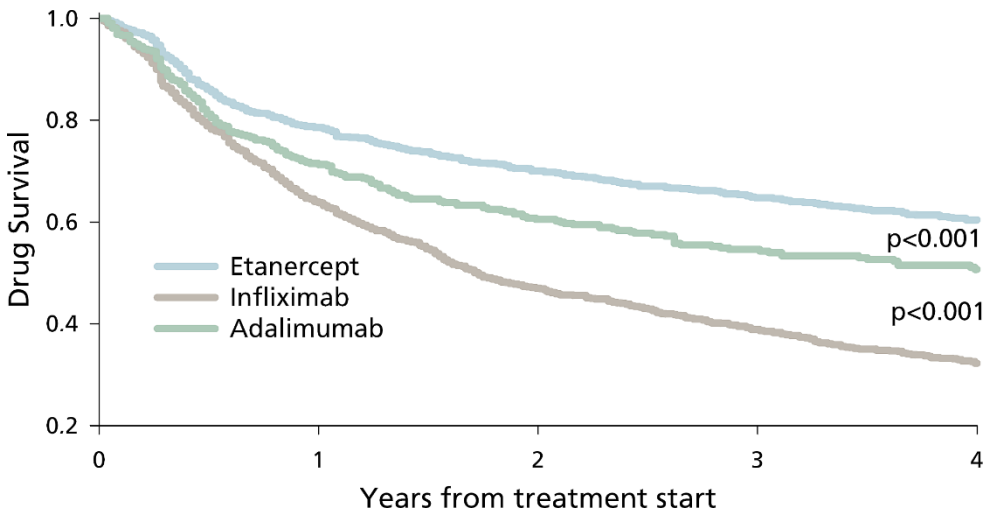


Figure 19. Drug survival in bio naïve patients in the SSATG
In total; 987, 912 and 415 patients started ETN, IFX and ADA respectively and 368, 610 and 195 stopped treatment during the first four years after treatment start. Log-Rank test p<0.001. Results from an all pairwise comparison procedure (Holm-Sidak method) are shown in the figure.

We compared bio naïve patients receiving ADA, ETN, or IFX. Survival on drug (Figure 19) gives the estimated fraction of patients on each drug at each time point. The results can be used to calculate the LUNDEX correction. At 12 months 11.9% of ETN, 11.8% of ADA, and 7.6% of IFX patients fulfilled the SR criteria, the difference ETN

vs IFX and ADA vs IFX being significant (p<0.05). After LUNDEX correction 7.2% of ADA, 8.8% of ETN patients, and 5.3% of IFX patients had achieved SR within the first 12 months of treatment.

The odds to achieve SR both within 12 months and during the first four years (HR) were higher when treated with ETN compared to IFX (Figure 20). ADA treated patients had higher HR to reach SR over the four years than IFX patients and had lower risk of escape at any time point during the first four years of treatment. No difference was seen between ADA and ETN.

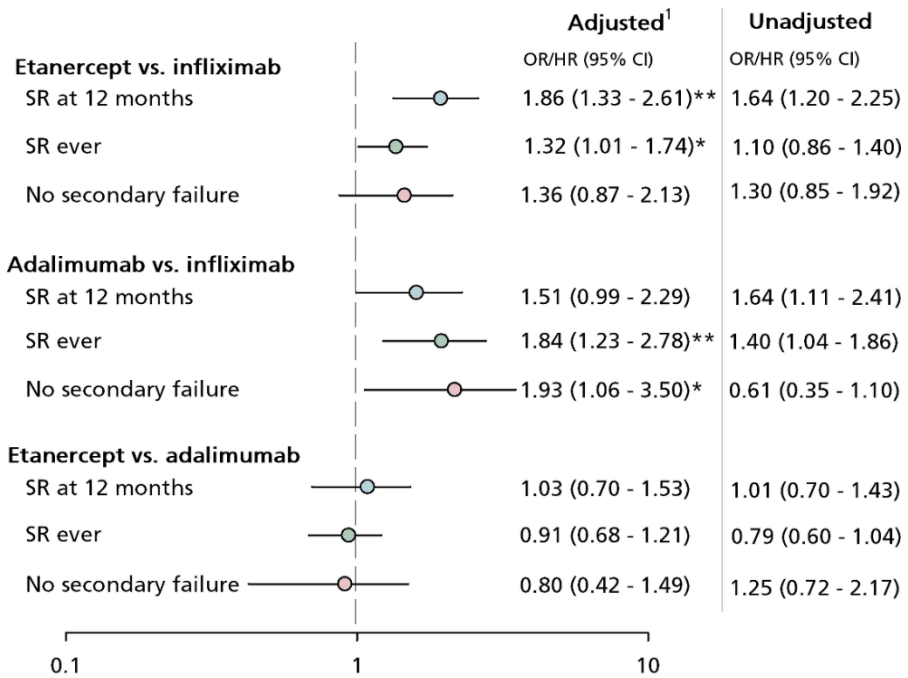


Figure 20. Response rates, drug comparison.
Blue: Odds of having achieved SR with first biologic after 12 months.
Green: HR for achieving SR with first biologic in the first 4 years of treatment.
Pink: HR for continued remission without secondary failure within 4 years.
Higher OR/HR favours drug to the left. On the right the results for the unadjusted analyses are presented. * p < 0.05. ** p < 0.005.
[1] Adjusted for those baseline variables that significantly changed the unadjusted or raw model.

Very notable was that once in SR patients stayed in remission. Patients on ADA had lower risk of escape during the first four years but patients with the longest SR were patients on IFX.

We have corrected for baseline characteristics but confounding by indication, channelling- and observation bias or other unmeasured confounders such as radiographic changes, comorbidity or compliance cannot be completely ruled out.

Variations in baseline data indicate that the anti-TNF treatments are used differently. IFX patients had numerically slightly higher age, disease duration, CRP, HAQ, and DAS28 at baseline. IFX is given as an intravenous treatment, patients have to come to the clinic as opposed to injecting ADA or ETN subcutaneously at home. When there is risk of lack of compliance physicians might lean towards the former method. Patients receiving IFX were scored on the day of infusion, this is the day of the treatment cycle that the patients is most likely to have lowest disease activity. When in true SR this should not matter but this possibly favours the other drugs.

On the other hand higher percentage of IFX treated patients received concomitant prednisolone and MTX or other DMARD compared to both ETN and ADA. Earlier linkage to an in-hospital discharge register with the same patient cohort showed no baseline difference in prior diabetes, malignancies, chronic pulmonary diseases, and cardiovascular diseases when comparing patients treated with ETN or IFX (128).

General discussion

Observational studies and randomised controlled trials

Randomised controlled trials (RCT), when appropriately designed, conducted, and reported, represent the gold standard in evaluating medical intervention, e.g. to prove drug efficacy, and are often necessary to determine the frequency of common adverse events (170). Double-blind trials are particularly effective in minimising biases inherent to observational studies, this in-built design controls for confounders, both known and unknown. But RCTs have limitations; the study periods are shorter (usually ≤1 year), most are relatively small, uncommon long term side effects are not registered, and the patient groups are often homogenous and may lack external validity (171,172). In a late RA cohort monitored over the long term in a weekly academic rheumatology clinic in Finland, 7 of 138 patients (5%) met the inclusion criteria for a RCT comparing anti-TNF treatments (172). In a recent comparison with RCTs, RA patients in observational studies were older, disease duration was longer, a higher number of different DMARDs were administered before starting biologic treatment and disease activity was lower at baseline (173). Over time, baseline DAS28 and HAQ declined in patients included in RCTs but not in patients from observational databases. RCTs utilise flare design, and regression towards the mean and the patient selection process is biased towards greater responsiveness, therefore drug efficacy in RCTs cannot be adapted to real life settings (174).

Observational studies involve research on subjects in a real-life, non-randomized setting. This thesis is based on cohort studies but other designs include case-control, and cross-sectional studies. Much of the research into the cause of diseases relies on this kind of study design, observational studies are often necessary when researching long term benefits and harms of medical interventions, e.g. rare or late adverse effects of treatments (175). Certain confounders or bias are inherent in cohort studies and can distort the apparent effect of the intervention of interest. Some confounders are known and these are sometimes possible to adjust for but adjusting for unknown or unmeasured confounders is not possible. Observational studies are recognised to be prone to three broad types of bias, including selection bias, information bias, and confounding (176). Selection bias occurs when there is a systematic difference between either (i) those included in a study or register and those not, (ii) those in the treatment

arm and those in the control group. This kind of bias might have occurred in this thesis when comparing different anti-TNF treatments. Patients treated with IFX, the only anti-TNF treatment given intravenously, differed from ADA and ETN in some aspects. This could be called confounding by indication, physicians tend to prescribe this kind of treatment to patients were there is risk for non-compliance. Information bias refers to measurement error, or difference in measurement quality (accuracy)(176). Patients receiving IFX were scored (DAS28, HAQ etc.) on the day of infusion by different evaluators every time, while patients receiving ETN and ADA were scored at scheduled physicians visits, often by the same physician. This can lead to information bias.

Coverage/completeness

Apart from biases inherited in observational studies our cohorts have some limitations. Although the SRQ is a nationwide register the 'completeness' of RA patients is not perfect. Since 2012 all rheumatology units from every region in Sweden contribute in a varying degree. In a report from the National Board of Health and Welfare, the completeness of patients with active RA was estimated to be 75%[1] in 2013 but 83% in 2016 (162). The completeness of a chronic disease like RA is not easy to estimate, partly since there is no clear date for onset of disease (unlike for a stroke for instance), and partly because there is risk for overestimation when deciding the true national prevalence. The specificity and sensitivity of the RA capture mechanism used by the National Patient Register is somewhat limited, based on registered diagnosis in specialist care. Using the ACR 1987 criteria as reference, a false-positive rate of around 6–15% has been estimated (5). Patients with RA are typically diagnosed and treated by rheumatologists rather than by general practitioners in Sweden, the opposite would lead to underestimation of the prevalence. The SRQ has only existed in its present form since 2012 and before that the completeness was much lower. Importantly, the coverage of each of SRQ sub-cohorts was good, for instance covered SSATG over 90% of all RA patients on biologics.

Many patients had no, or only 1-2 registered visit in SRQ and were therefore excluded from paper III and IV. Those excluded hade different demographics were more often males and older ($p<0.001$) but because of limited data we cannot analyse this group further. The registry does not include any data from patients prior to inclusion, which impacts especially analysis on patients with disease onset prior to 1992. This might lead to underestimation of the frequency of SR in this group, to minimise the risk we only used patients with symptom duration of 2 years of less for parts of the analysis.

[1] Completeness as calculated by the National Board of Health and Welfare:
Completeness=SRQ/(SRQ + patients only in the National Patient Register)

Selection of remission criteria

The use of DAS28 remission criteria is often criticised, but in the observational setting with patients with long standing disease, it seems sensible to use these criteria. They probably represents minimal disease activity rather than true remission and we have previously described how the definition allows for several tender and swollen joints. Using a treatment target like the SDAI or CDAI remission in established RA which around 10% will reach is not practical and might lead to overtreatment in this setting. As our results indicate that is it not the selection of remission criteria that is most important but rather the maintenance of a steady state of low disease activity. This thesis covers the period from the time where MTX came to be the anchor drug in RA treatment and the early biologic years, it has taken a lot of catching up and a large fraction of the patients have irreversible structural damage with impaired physical function. For future studies covering RA patients with early diagnosis and treated to target of no swollen joints, DAS28 remission will probably not be suitable.

When starting this work there were almost no studies on SR, and no established time criteria. Our time frame of at least a 6-month duration is arbitrary but reasonably practical when it comes to patients in the observational setting since a visit at 6-month intervals are usually part of the schedule in Sweden, at least during the first years.

Conclusions

- In an observational setting in Sweden, only half of patients experience SR within 5 years from symptom onset.
- The prevalence of SR increases during the first disease years and peaks at about five years.
- Patients with established RA starting anti-TNF treatment who reach SR do so within the first two years. Concomitant methotrexate is positively associated with SR.
- Once in SR patients remain in remission for a substantial period of time.
- Compared to patients that only reach remission occasionally, patients in SR have better physical function over time.
- The sustainability of remission is a more important treatment goal than aiming at fulfilling stricter remission criteria. Maintenance of remission should be a treatment goal in RA.
- Milder disease, better physical function, absence of ACPA, male sex and lower age at disease onset are associated with SR.
- Early RA, defined as less than 6 months from symptom onset to diagnosis is strongly positively associated with SR
- There is a clear secular trend towards increased incidence of SR in patients with RA in Sweden -most probably reflecting adherence to national and international guidelines recommending early treatment start and the "treat to target" approach.

Future perspectives

RA is a chronic inflammatory disease of unknown cause/causes and research on finding it/them is an ultimate goal for the future. Increasing knowledge of the pathogenesis in RA have led to several effective DMARDs including modern biological treatment and small molecules and thus remission has become a realistic treatment goal.

Sustained remission (SR) is probably the best way to reach the primary goal of treating patients with RA; to maximise long-term health-related quality of life. Despite the progress that has been made during that time there is still a lot to be done. Even in the most ideal of situations where patients present early and start specific therapy early; the majority will require lifelong DMARD treatment and has high risk of worse physical function and lower participation in social and work-related activities. The immune response that eventually becomes RA probably starts years before symptom onset, but today we do not have the diagnostic tools that allow us to predict which patient with arthralgia or pre-arthralgia will develop chronic arthritis. So the development of diagnostic tools that allows for the detection and possible treatment in the preclinical phase of RA is definitely something to aim for.

With the current knowledge there are some strategies that need to be implemented generally in our health care system:

- Strategies that enable general practitioners to recognise and refer patients earlier. This mostly mean implementing current knowledge and educating physicians.
- Triage clinics where patients with arthralgia can refer themselves for a short but thorough consultation with a specialist.
- After being diagnosed with early RA, the patient should be followed tightly in an 'early arthritis' program and treated to the target of sustained remission.
- The program should include an educational program led by physiotherapist, occupational therapist and nurse, with focus on lifestyle factors, including smoking, as well as coping strategies.

The concept of remission has changed over time. From the time when DAS28 <2.6 was considered sufficient to the present time where there is no tolerance for swollen joints, but still there is not a reliable definition available. There is an abundance of

instruments and variables available for the assessment of disease activity in RA, but most of these combine two different sides of the disease; objective inflammation and subjective experience. These two sides are treated in different ways. The main idea behind the change in RA management in recent years is the early and consistent reduction in inflammation as mentioned earlier.

Patient reported measures can blur the results of the composite DAIs in the individual patients, e.g. the patient with high isolated pain but no inflammation. Remission as defined today is not a realistic treatment goal in these patients. Modified remission criteria or modified disease activity score should therefore be on the agenda to be used for specific purposes. However in the context of the 'shared decision model' in RA it is still important to include the subjective measures.

Observational studies will continue to provide valuable information on important outcomes such as SR. More specifically the research agenda includes:

- To investigate frequency of SR in patients treated with different treatment strategies
- To examine if target specific treatment goals such as aiming for SR results in more patients in SR
- Long term effect of SR on morbidity and mortality
- Frequency and predictors of drug-free sustained remission

No matter which definition used, SR may lead to withdrawal of biologic treatments and tapering of sDMARD. There are already some clinical studies investigating drug-free SR. Many escape and require treatment, but those that stay in drug-free remission have possibly re-established their immune system or are effectively cured. More and more interest on research is aimed at secondary prevention, where individuals with arthralgia suspicious for progression to RA are treated before any signs of arthritis. The next step would be primary prevention, where seropositive individuals with genetic risk factors are immunized. That is the future. As for now the aim should be to reach and maintain remission in patients with RA.

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Appendices

A. Baseline data SSATG, to be filled out by the treating physician.

B. Patient form SSATG, filled out at each visit. Includes pain VAS, and PtGA. On reverse, the Swedish version of the HAQ.

C. Visit form SSATG, filled out by physician at each visit.

D. Security form SSATG, filled out by patient at each visit. On reverse, physicians comments.

E. Example of a feedback given regularly from SSATG to treating physician.

F. SRQ screenshot showing a timeline of a difficult to treat patients. On reverse, visit form SRA, filled by the physician.

 SSATG

Basdata för DMARD- biologisk behandling

Personnr:

Appendix A

Namn:

- Inklusionsdatum:.....
- Pat ansvarig läkare……..
- ***Behandlings regim:***

  Preparat:.....

  Planerad underhållsbeh……

  Kombination (med annat DMARD) ❑ ⟶ Tillägg till tidigare DMARD Ja ❑ Nej ❑

  Monoterapi (ej annat DMARD) ❑

- ***Subjektiv destruktions- ankylosgradering:***

  Mindre destruktiv/ankyloserande sjukdom ❑ Kraftigt destruktiv/ ankyloserande sjd ❑

- ***Behandlingsdiagnos och debutår/månad (ÅÅÅÅ/MM):***

  RA ❑ ..... År/mån ……ICD10nr……

  Annan ❑ Vilken?..... År/mån.....ICD10nr……

- ***Indikation:***
  (endast 1 alternativ)

  Svikt / Intolerans på DMARD
  (avser någonsin, inklusive biologiskbeh)

  - på DMARD i komb.beh oavsett antal ❑
  - på >3 DMARD prep…… ❑
  - på 3 DMARD prep…… ❑
  - på 2 DMARD prep…… ❑
  - på 1 DMARD prep…… ❑

  Inflam. aktiv *ej tidigare* DMARD beh ❑

  Pats önskemål (ovanstående stämmer ej) ❑

- ***Patientens egna uppgifter om längd ……cm och vikt……kg***

- ***Tidigare/pågående DMARD beh :*** ❑ **Nej** ❑ **Ja,** kryssa för vilka nedan

❑ Antimalaria	❑ Leukeran
❑ Arava	❑ MabThera
❑ Azatioprin	❑ Metotrexat
❑ Ciklosporin	❑ Orencia
❑ Cimzia	❑ Penicillamin
❑ Cyklofosfamid (inkl. Sendoxan)	❑ Podofyllotoxin prep (inkl. Reumacon)
❑ Enbrel	❑ Remicade
❑ Entocort	❑ RoActemra
❑ Guld i.m	❑ Salazopyrin
❑ Guld p.o	❑ Simponi
❑ Humira	❑ .....
❑ IVIG	❑ .....
❑ Kineret	❑ .....

OBS!!! Fortsättning på baksidan

- ***För <u>ALLA</u> RA/polyartritpatienter*** ***Nej*** ***Ja***

Morgonstelhet	❑	❑	(≥1 timme)
Artrit i ≥ 3 ledområden	❑	❑	(PIP, MCP, handled, armbåge, knä, fotled, MTP – hö eller vä)
Artrit i hand	❑	❑	(PIP, MCP, handled)
Symmetrisk artrit	❑	❑	(symmetri mellan ledområden – hö och vä sida)
Reumatiska noduli	❑	❑	

			Vet ej - irrelevant	
Reumatoid faktor	❑	❑	❑	
Anti-CCP	❑	❑	❑	
Röntgenförändringar	❑	❑	❑	(usurer el. otvetydig periartikulär osteopeni i <u>hand</u>skelett)

- ***För nydebuterad RA/polyartrit <u>ÄVEN</u>*** ***Nej*** ***Ja***

Minst 1 svullen led	❑	❑	
RF eller Anti-CCP> 3ggr över ref. gräns	❑	❑	
Duration av synoviter ≥6 veckor	❑	❑	
Förhöjd CRP eller SR	❑	❑	
Antal engagerade[#] **stora/medelstora leder**	……		(axel, armbåge, handled, höft, knä, fotled)
Antal engagerade[#] **små leder**	……		(fingerled, Mtf, tåled)

[#] Svullna och/eller ömma

- ***För spondylartriter*** [*] ***Nej*** ***Ja*** **Vet ej - irrelevant**

Säker ankyloserande spondylit[**]	❑	❑		
Tidigare/aktuell klinisk spondylit/sacroiliit	❑	❑		
Perifer artritsjukdom (dist. om axlar och höfter)	❑	❑		
Uveit (någonsin)	❑	❑		
HLA-B27	❑	❑	❑	
Hereditet för spondartrit/psoriasis	❑	❑	❑	
Radiologisk sacroiliit	❑	❑	❑	
Radiologisk spondylit	❑	❑	❑	
Tidigare/aktuell klinisk daktylit	❑	❑	❑	
Tidigare/aktuell klinisk entesit	❑	❑	❑	
Tidigare/aktuell psoriasis	❑	❑	❑	
		↳	Nagelpsoriasis ❑	PPP ❑
IBD (inflammatory bowel disease)	❑	❑		
		↳	Debut år……	Mb Crohn ❑ Ulcerös Colit ❑
				Annan ……..

[*]**Kriterier för spondylartropati enligt ESSG (European Spondylarthropathy Study Group)**
Inflammatorisk ryggsmärta eller perifer synovit (asymmetrisk, huvudsakligen i nedre extremiteterna) och en av följande:

- Hereditet
- Psoriasis
- Inflammatorisk tarmsjukdom
- Uretrit, cervicit eller akut diarré inom en månad före artrit debut
- Glutealsmärta alternerande mellan vänster och höger sida
- Entesopati
- Sacroiliit (röntgenologisk)

[**]**Modifierade NewYork-kriterier (1984) för ankyloserande spondylit (AS)**
1. Ländryggsvärk under minst tre månader som förbättras av rörelse men ej av vila.
2. Begränsad rörlighet i ländryggen sagitalt (framåt och bakåt) och frontalt (i sidled).
3. Minskad bröstkorgsexpansion (ålders- och könsjusterat).
4. Bilateral sakroiliit grad II-IV eller unilateral sakroiliit grad III eller IV.

Fotnot: Definitivt AS föreligger vid kriterium 4 och minst en av punkt 1-3.

Reumatologiska kliniken, Lund, 080430/LL **SSATG**

PATIENTBLANKETT

Datum:.....

Ange din vikt: …….……Kg

Svara på frågorna här nedan och på baksidan.
Var noga med att läsa varje fråga och instruktionen.
Tack för din hjälp.

Personnr:

Namn:

Appendix B

Sätt ett streck tvärs över linjen under frågan hur du har upplevt den senaste veckan:

Hur mycket smärta har du haft på grund av din ledsjukdom?

0 1 2 3 4 5 6 7 8 9 10

Ingen smärta alls ——— Värsta tänkbara smärta

Hur har du känt dig, allmänt sett, med tanke på din ledsjukdom?

0 1 2 3 4 5 6 7 8 9 10

Helt bra ——— Så dålig som tänkas kan

Markera genom att kryssa i en ruta, vilket påstående som bäst beskriver ditt hälsotillstånd idag.

Rörlighet

Jag går utan svårigheter	❑	Kryssa
Jag kan gå men med viss svårighet	❑	endast
Jag är sängliggande	❑	i en ruta

Hygien

Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning	❑	Kryssa
Jag har vissa problem att tvätta eller klä mig själv	❑	endast
Jag kan inte tvätta eller klä mig själv	❑	i en ruta

Huvudsakliga aktiviteter (tex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

Jag klarar av min huvudsakliga sysselsättning	❑	Kryssa
Jag har vissa problem med att klara av min huvudsakliga sysselsättning	❑	endast
Jag klarar inte min huvudsakliga sysselsättning	❑	i en ruta

Smärtor/besvär

Jag har varken smärtor eller besvär	❑	Kryssa
Jag har måttliga smärtor eller besvär	❑	endast
Jag har svåra smärtor eller besvär	❑	i en ruta

Rädsla/nedstämdhet

Jag är inte orolig eller nedstämd	❑	Kryssa
Jag är orolig och nedstämd i viss utsträckning	❑	endast
Jag är i högsta grad orolig eller nedstämd	❑	i en ruta

Jämfört med mitt allmänna hälsotillstånd de senaste tolv månaderna är mitt hälsotillstånd i dag:

Bättre	❑	Kryssa
Oförändrat	❑	endast
Sämre	❑	i en ruta

Är ditt nuvarande tillstånd tillfredsställande vad gäller din allmänna funktionsnivå och de smärtor du har nu?

Ja ❑ Nej ❑

Funktionsfrågeformulär

SRF 1996:1

Datum _____

Sätt ett kryss i den ruta som bäst beskriver Din situation under den senaste veckan	Utan svårighet	Med viss svårighet	Mycket svårt	Använder hjälpmedel	Hjälp av annan person	Kan inte alls	
Kan Du tvätta håret?	❑	❑	❑	❑	❑	❑	
Kan Du klä på Dig, inklusive knyta skoband och knäppa knappar?.....	❑	❑	❑	❑	❑	❑	____
Kan Du resa Dig från en stol som saknar armstöd?.....	❑	❑	❑	❑	❑	❑	
Kan Du komma i och ur sängen?.....	❑	❑	❑	❑	❑	❑	____
Kan Du skära kött?	❑	❑	❑	❑	❑	❑	
Kan Du laga Din egen mat?	❑	❑	❑	❑	❑	❑	
Kan Du lyfta ett fullt glas till munnen?.	❑	❑	❑	❑	❑	❑	____
Kan Du gå ned för fem trappsteg?.....	❑	❑	❑	❑	❑	❑	
Kan Du gå utomhus på plan mark?.....	❑	❑	❑	❑	❑	❑	____
Kan Du bada i badkar?	❑	❑	❑	❑	❑	❑	
Kan Du sätta Dig på och resa Dig från en toalettstol?	❑	❑	❑	❑	❑	❑	
Kan Du tvätta och torka Dig överallt?	❑	❑	❑	❑	❑	❑	____
Kan Du ta ned ett 2kg paket med t.ex. socker från en hylla i huvudhöjd?.....	❑	❑	❑	❑	❑	❑	
Kan Du böja Dig ned och ta upp kläder från golvet?	❑	❑	❑	❑	❑	❑	____
Kan Du öppna bildörrar?	❑	❑	❑	❑	❑	❑	
Kan Du öppna burkar med skruvlock, som varit öppnade förut?.....	❑	❑	❑	❑	❑	❑	
Kan Du vrida på en vanlig vattenkran?	❑	❑	❑	❑	❑	❑	____
Kan Du dammsuga?	❑	❑	❑	❑	❑	❑	
Kan Du klara Dina inköp till hushållet?	❑	❑	❑	❑	❑	❑	
Kan Du komma i och ur en bil?.....	❑	❑	❑	❑	❑	❑	____

1/0,13 **2**/0,25 **3**/0,38 **4**/0,5 **5**/0,63 **6**/0,75 **7**/0,88 **8**/1,0 **9**/1,13 **10**/1,25 **11**/1,38 **12**/1,5 **13**/1,63
14/1,75 **15**/1,88 **16**/2,0 **17**/2,13 **18**/2,25 **19**/2,38 **20**/2,5 **21**/2,63 **22**/2,75 **23**/2,88 **24**/3,0

SSATG

Appendix C

Besöksblankett – DMARD- biologisk behandling

Evalueringsdatum:…….

Läkare vid besöket:……..…..

Personnr:

Namn:

Licensnr:

• *Aktuell sjukdomsaktivitet <u>alla</u> diagnoser*

Allmän hälsa	Smärta	HAQ	SR	CRP	Leder svullna 28-leder	Leder ömma 28-leder

Läkar-/eval bedömning → Ingen ❑ Låg ❑ Måttlig ❑ Hög ❑ Maximal ❑

• *Medicinering*

Huvudterapi →	Genomsnittlig intagen dos (per dag eller vecka) under de senaste 2 veckorna, för längre dosintervall ex. *Remicade, MabThera mfl, anges senste dos och datum <u>före</u> aktuell evaluering*	Ordinerad dos mg och frekvens ex. 200mg var 8:e vecka, 40mg v a v, 25mg 2ggr/v, 50mg 1ggr/v, 100mg/d
……..……..	……..…..mg/…….....	……..…..mg/…….....
DMARD Nej ❑ Ja ❑ →		
……..……..	……..…..mg/…….....	……..…..mg/…….....
……..……..	……..…..mg/…….....	……..…..mg/…….....
……..……..	……..…..mg/…….....	……..…..mg/…….....
System steroider	Nej ❑ Vb ❑ Ja ❑ ….....mg	Nej ❑ Vb ❑ Ja ❑ ….....mg
NSAID Cox1 ❑ Cox2 ❑	Nej ❑ Vb ❑ Ja ❑	Nej ❑ Vb ❑ Ja ❑
Analgetika	Nej ❑ Vb ❑ Ja ❑	Nej ❑ Vb ❑ Ja ❑

• *För Spondartriter inklusive Psoriasisartrit <u>dessutom</u>*

Leder svullna 66-leder	Leder ömma 68-leder	PASI-Score (ev.)

Klinisk pågående:	Nej	Ja	Ej relevant	
Spondylit	❑	❑	❑	
Daktylit	❑	❑	❑	
Entesit	❑	❑	❑	
Nagel psoriasis	❑	❑	❑	
PPP (palmo-plantar-pustulos)	❑	❑	❑	
			Hö	Vä
Infl. reumatisk ögonsjd (uveit, sclerit, keratit)	❑	❑ →	❑	❑

Antal akuta uveiter sedan föregående evaluering ……..……..

Om pågående/tidigare klinisk spondylit skall pat fylla i föjande formulär

	Nej	Ja
BASDAI	❑	❑
BASFI	❑	❑
BASG1+G2	❑	❑

Registreringsanvisningar vid DMARD- biologisk behandling

Denna Besöksblankett skall fyllas i vid insättningen och sedan vid 3, 6 och 12 månader, samt därefter var 6:e månad, eller så snart behandlingen avbryts oavsett orsak. Vissa preparat har tätare evalueringsintervall.

Patientblanketten fylls i av patienten på båda sidorna inför läkarbesöket, frågorna är självinstruerande. Läkaren räknar ut värdet för HAQ på sidan två, genom att kryss i den första kolumnen ger poäng =0, den andra poäng = 1, den tredje till femte kolumnen poäng = 2 och den sista kolumnen = 3 poäng. Varje grupp med frågor poängsätts på strecket till höger efter den högsta poängen på någon fråga i gruppen. Om patienten t.ex. behöver hjälp med att tvätta håret (=2) räknas detta ut till höger, även om patienten inte har några svårigheter att klä sig (=0). Poängen från varje frågegrupp till höger (0-3) summeras, och summan blir då mellan 0 och 24, varefter ett genomsnitt räknas ut enligt lathunden längst ned, t.ex. ger summan 11 ett HAQ på 1.38.

Effektregistreringen på denna besöksblanketts framsida ***för alla diagnoser*** fylls i enligt:

LVnr/Personnummer = en unik patientkod i form av diarienummer på licensen/patientens personnr.
Patientnamn = Efternamn, förnamn
Datum = Undersökningsdatum
Läk Signatur = Vid evalueringstillfället behandlande läkare
Allmän hälsa = VAS värdet mätt i mm från vänster på skalan på patientblanketten, dvs ”Helt bra blir 0 och ”så dålig som tänkas kan” blir 100
Smärta = VAS värdet mätt på samma sätt från vänster på skalan
HAQ = värdet uträknat enligt ovanstående instruktion
SR = värdet i mm från laboratoriet
CRP = värdet från lokalt laboratorium.
Leder svullna = antalet svullna leder enligt 28-ledsindex, i vilket inkluderas följande leder:
10 PIP-leder, 10 MCP-leder, 2 handleder, 2 armbågsleder, 2 axelleder och 2 knäleder.
Leder ömma = antalet ömma leder enligt 28-ledsindex
Läkarbedömning med övriga variabler kända (de föregående rutorna på raden) gör läkaren en global bedömning av sjukdomsaktiviteten - kryssa för **ett** alternativ.

Medicinering – intagen och ordinerad vid besöket

Biologiskt läkemedel/DMARD anges med preparatnamn. Genomsnittlig veckodos senaste 2 veckorna anges i mg/dag eller vecka, för längre dosintervall än 2 veckor, exempelvis vid infusionsbehandling anges senaste dos och datum ex. 200mg 020405. Ordinerad dos anges i mg och frekvens ex. 200 mg var 8:e vecka, 40mg v a v, 25 mg 2ggr/vecka, 50mg1 ggr/vecka, 100mg/d.
Övrig medicinering besvaras med kryssrutor för intagen resp ordinerad varvid kortisondosen anges vid regelbunden medicinering, som dygnsdos i mg ekvivalent med Prednisolon.

För Spondartrit inklusive psoriasis

Bör även 66/68-ledsindex göras (OBS! Både 28-ledsindex och 66/68 ledsindex skall anges).
Eventuellt PASI-Score (http://www.medscape.com/viewarticle/507681_6)
Frågorna vid kryssrutorna besvaras med Ja, Nej eller Ej relevant
Om pågående/tidigare klinisk spondylit bör pat fylla i BASDAI, BASFI och eventuellt BASG1+G2

Lund 060313/LL

Säkerhetsformulär för patienter med antireumatisk behandling.

Personnr:

Appendix D

Namn:

Datum ……

Var vänlig och besvara nedanstående frågor *före* läkarbesöket genom att kryssa i Ja eller Nej, vid kryss i Ja rutan besvaras även följdfrågan. Lämnas sedan till läkaren/sjuksköterskan som Du träffar idag.

Har Du sedan föregående besök här på Reumatologen :

- Varit inlagd på sjukhus? Nej ❑ Ja ❑ Varför?.....
  Vilket sjukhus och vilken avdelning?.....
  ……
- Blivit opererad? Nej ❑ Ja ❑ Vilken operation? ……..
  ……
- Upplevt någon biverkning av Din behandling? Nej ❑ Ja ❑ Vad?.....
  ..…….....
  ……
- Haft någon infektion såsom:
  Halsont / snuva Nej ❑ Ja ❑
  Tandinfektion Nej ❑ Ja ❑
  Bältros Nej ❑ Ja ❑
  Hudinfektion Nej ❑ Ja ❑
  Lunginflammation Nej ❑ Ja ❑
  Maginfluenza Nej ❑ Ja ❑
  Urinvägsinfektion Nej ❑ Ja ❑
  Övrig infektion Nej ❑ Ja ❑ Vilken?……..……..
  ……

Skriv ev kommentarer på baksidan under rubriken patient kommentar

Patient kommentar

Läkarens kommentar

Datum	Händelse	Beskrivning av symptom, organengagemang, tidsrelation till huvudterapi, utredning samt ev slutenvård.

- **Allvarlighetsgrad (*= rapportskyldighet)**

❑ Mild
❑ Måttlig
❑ Allvarlig *
❑ Livshotande *
❑ Dödlig *
❑ Övrig rapportskyldighet *

- **Förlopp**

❑ Tillfrisknat utan men
❑ Tillfrisknat med men
❑ Okänt
❑ Ännu ej tillfrisknat
❑ Avliden

- **Relation till huvudterapi**

❑ Sannolik
❑ Möjlig
❑ Osannolik
❑ Ej bedömbart

- **Åtgärd huvudterapi**

❑ Ingen
❑ Tillfälligt utsatt från-till eller antal veckor….
……
❑ Definitivt utsatt

Skall skickas till Läkemedelsverket: Ja ❑ Avvakta ❑ Ej till LMV ❑

- **Avslutad terapi övrig orsak**

Huvudterapi: ……...Datum……..

❑ Uppnådd effekt avtagit ❑ Terapisvikt ❑ Övrigt ……..

……....

Appendix E

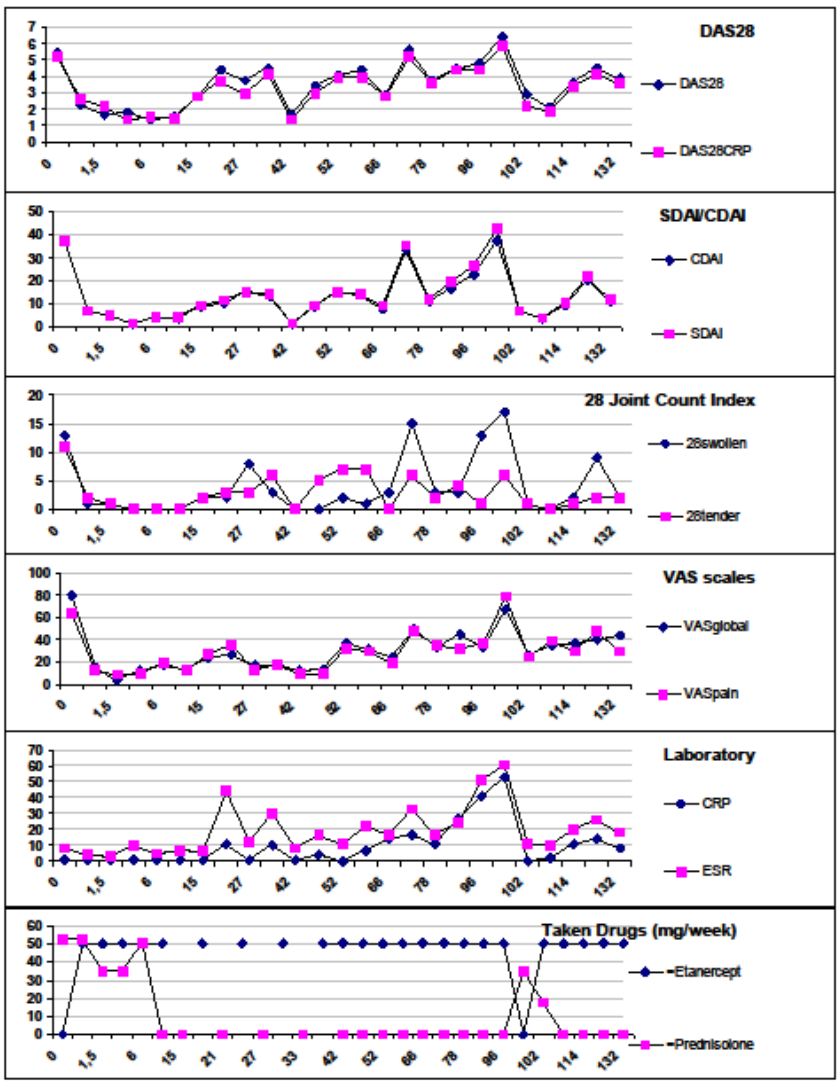
Cohort treatment	Enbrel inj
Responsible	
Centre	Trelleborg_Sweden
IntroTime	2000-01-26
ExitTime	
StopCause	
FUmonth/date	132 2011-01-19

Response criteria	20%	50%	70%
ACR	1	0	0
EvalGlobal	1	1	0
VASglobal	1	0	0
VASpain	1	1	0
Prednisolone	1	1	1

response	good	moderate	none
EULAR (DAS)	0	1	0

Disease state/activity	severe	moderate	mild	remission
DAS28	0	1	0	0
SDAI	0	1	0	0
CDAI	0	1	0	0

HAQ improvement	>0.22	>0.5
HAQ reduction	1	0



Fulfillment of response and disease activity criteria and graphics of variables

Cohort treatment	**Enbrel inj**
Responsible	
Centre	**Trelleborg_Sweden**
IntroTime	**2000-01-26**
ExitTime	
StopCause	
FUmonth/date	**132** **2011-01-19**

Response criteria

	20%	50%	70%
ACR	1	0	0
EvalGlobal	1	1	0
VASglobal	1	0	0
VASpain	1	1	0
Prednisolone	1	1	1

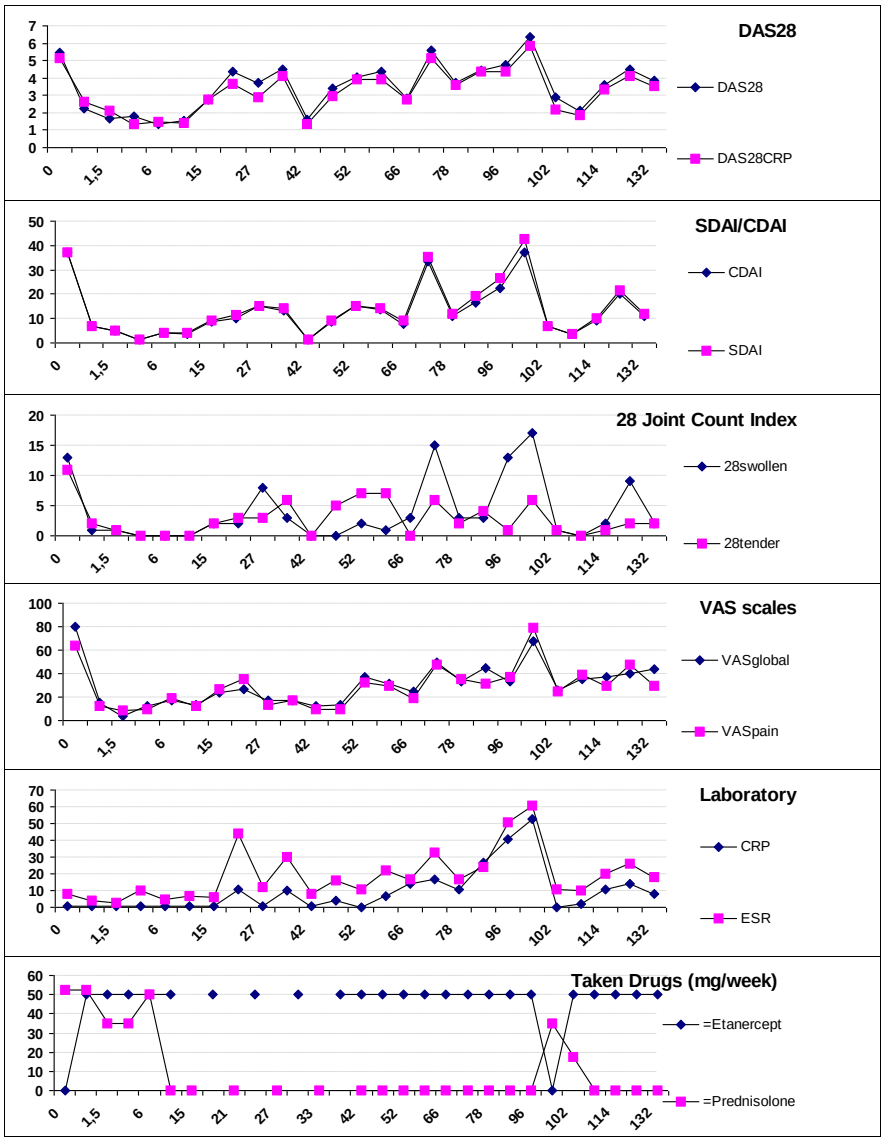
response	good	moderate	none
EULAR (DAS)	0	1	0

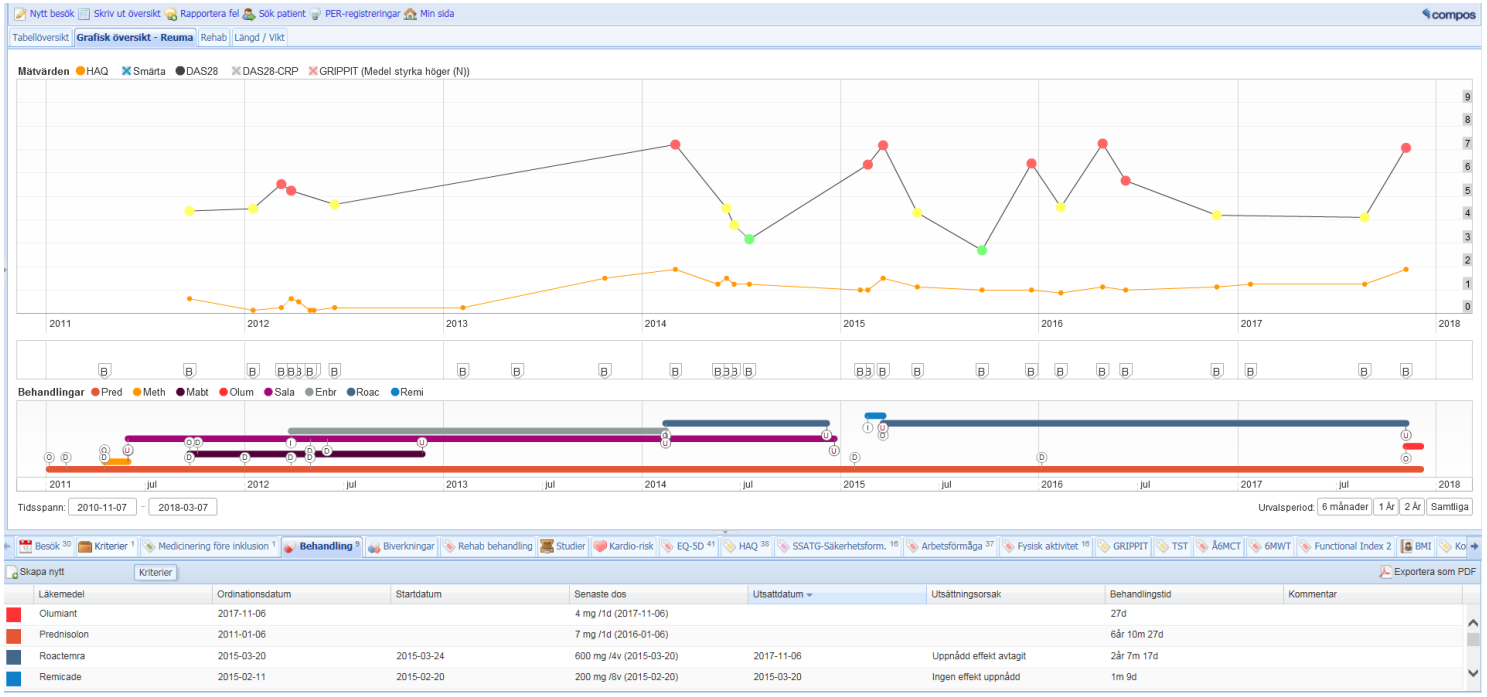
Disease state/activity

	severe	moderate	mild	remission
DAS28	0	1	0	0
SDAI	0	1	0	0
CDAI	0	1	0	0

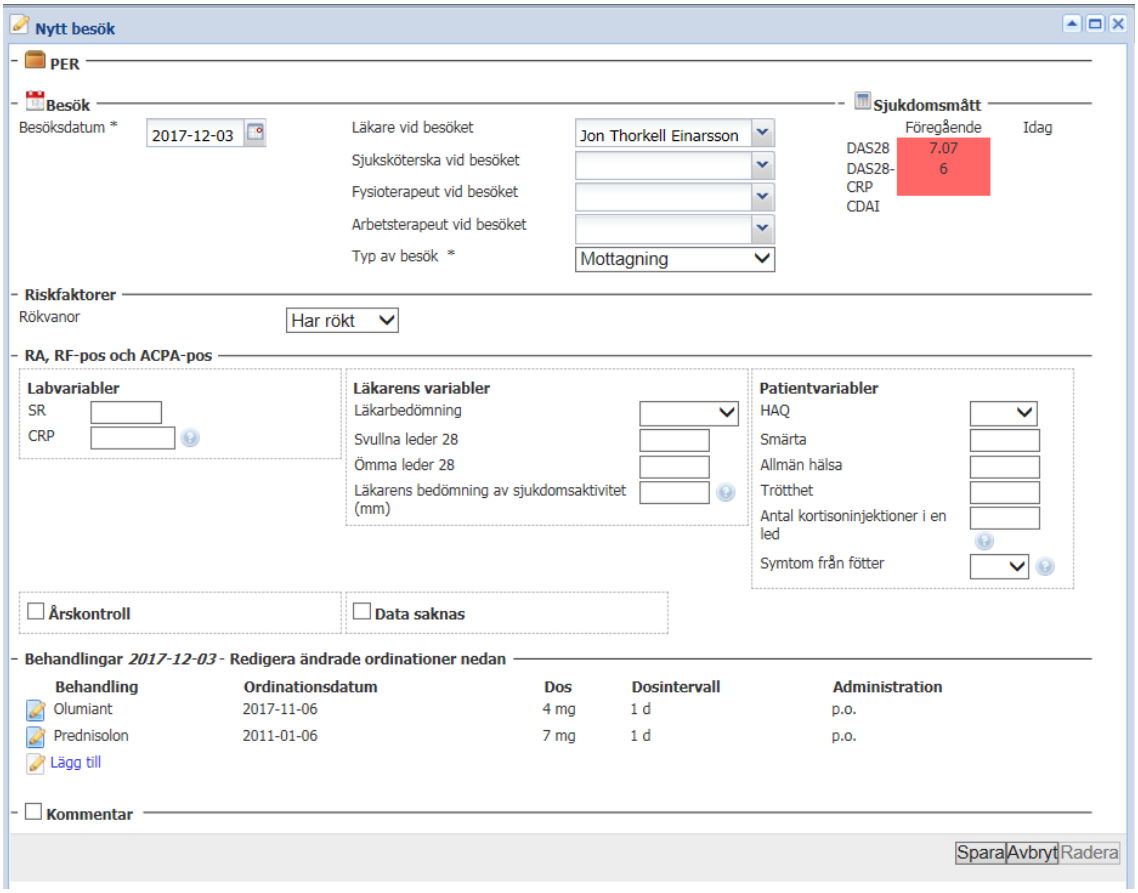
HAQ improvement

	>0.22	>0.5
HAQ reduction	1	0




Nytt besök
Skriv ut översikt
Rapportera fel
Sök patient
PER-registreringar
Min sida
compos
Tabellöversikt
Grafisk översikt - Reuma
Rehab
Längd / Vikt
Mätvärden HAQ Smärta DAS28 DAS28-CRP GRIPPIT (Medel styrka höger (N))
2011 2012 2013 2014 2015 2016 2017 2018
Behandlingar Pred Meth Mabt Olum Sala Enbr Roac Remi
Tidsspann: 2010-11-07 - 2018-03-07
Urvalsperiod: 6 månader 1 År 2 År Samtliga
Besök 30
Kriterier 1
Medicinering före inklusion 1
Behandling 9
Biverkningar
Rehab behandling
Studier
Kardio-risk
EQ-5D 41
HAQ 38
SSATG-Säkerhetsform. 16
Arbetsförmåga 37
Fysisk aktivitet 16
GRIPPIT
TST
Å6MCT
6MWT
Functional Index 2
BMI
Skapa nytt
Kriterier
Exportera som PDF
Läkemedel
Ordinationsdatum
Startdatum
Senaste dos
Utsättdatum
Utsättningsorsak
Behandlingstid
Kommentar
Olumiant 2017-11-06 4 mg /1d (2017-11-06) 27d
Prednisolon 2011-01-06 7 mg /1d (2016-01-06) 6år 10m 27d
Roactemra 2015-03-20 2015-03-24 600 mg /4v (2015-03-20) 2017-11-06 Uppnådd effekt avtagit 2år 7m 17d
Remicade 2015-02-11 2015-02-20 200 mg /8v (2015-02-20) 2015-03-20 Ingen effekt uppnådd 1m 9d

Appendix F


Nytt besök
PER
Besök
Besöksdatum *
2017-12-03
Läkare vid besöket
Jon Thorkell Einarsson
Sjuksköterska vid besöket
Fysioterapeut vid besöket
Arbetsterapeut vid besöket
Typ av besök *
Mottagning
Sjukdomsmått
Föregående
Idag
DAS28
7.07
DAS28-CRP
6
CDAI
Riskfaktorer
Rökvanor
Har rökt
RA, RF-pos och ACPA-pos
Labvariabler
SR
CRP
Läkarens variabler
Läkarbedömning
Svullna leder 28
Ömma leder 28
Läkarens bedömning av sjukdomsaktivitet (mm)
Patientvariabler
HAQ
Smärta
Allmän hälsa
Trötthet
Antal kortisoninjektioner i en led
Symtom från fötter
Årskontroll
Data saknas
Behandlingar 2017-12-03 - Redigera ändrade ordinationer nedan
Behandling
Ordinationsdatum
Dos
Dosintervall
Administration
Olumiant
2017-11-06
4 mg
1 d
p.o.
Prednisolon
2011-01-06
7 mg
1 d
p.o.
Lägg till
Kommentar
Spara
Avbryt
Radera

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