APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

6ª Edizione

GERIATRIA E MALATTIE REUMATICHE

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DMARDs convenzionali sintetici

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Disease modifying antirheumatic drugs (DMARDs)

- Farmaci che hanno dimostrato di alterare il decorso naturale della RA (ad es. ritardare o prevenire il danno articolare e /o migliorare la funzionalità)
- Variano ampiamente fra loro per tipo, meccanismo di azione, rapidità d'azione e profilo di tossicità.
- Uso aumentato dagli anni '90 (salvo penicillamina e Sali d'oro)

Kremer JM et al, 2002 ; JR, Haire CE, et al. 1996 ; O'Dell JR. et al 1996; Boers M, et al, 1997; Mottonen T, et al. 1999 Goekoop-Ruiterman YP, et al. 2005, Veena K et a, 2007

DMARDs

Agent	Time to benefit	Potential for toxicity	Toxicities to monitor
Methotrexate	1–2 months	Moderate	Myelosuppression, hepatic fibrosis and cirrhosis, pulmonary infiltrates
Hydroxychloroquine	2–6 months	Low	Macular damage
Leflunomide	4–12 weeks	Low	Diarrhea, alopecia, rash, headache, risk of immunosuppression infection
Sulfasalazine	1–3 months	Low	Myelosuppression
Cyclosporine	4–8 weeks	High	Renal insufficiency, hypertension
Gold, oral	4–6 months	Low	Myelosuppression, proteinuria
Gold, parenteral	3–6 months	Moderate	Myelosuppression, proteinuria
Azathioprine	2–3 months	Moderate	Myelosuppression, hepatotoxicity, lympho-proliferative disorders
Minocycline*	1–3 months	Low	Hyperpigmentation, dizziness, vaginal yeast infections, lupus

* Not approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis.
SOURCE: ACR 2002

Smolen SJ et al, 2017

PZ “senior”

- ≥ 60 aa
- Popolazione esclusa dalle sperimentazioni
- Differenti farmacodinamica e farmacocinetica
- Possibili risposte alterate
- Alterato assorbimento (riduzione secrezione salivare, succhi gastrici, motilità intestinale)
- Alterate distribuzione e metabolismo: incremento ponderale, riduzione del tessuto sottocutaneo, disidratazione, ridotta gittata, ridotto flusso ematico renale ed epatico, ridotta sintesi proteica, clearance
- Maggiore suscettibilità alle infezioni e comorbidità misconosciute
- Politerapia
- Disturbri psichiatrici e fragilità psichica
- Aderenza

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ORIGINAL ARTICLE

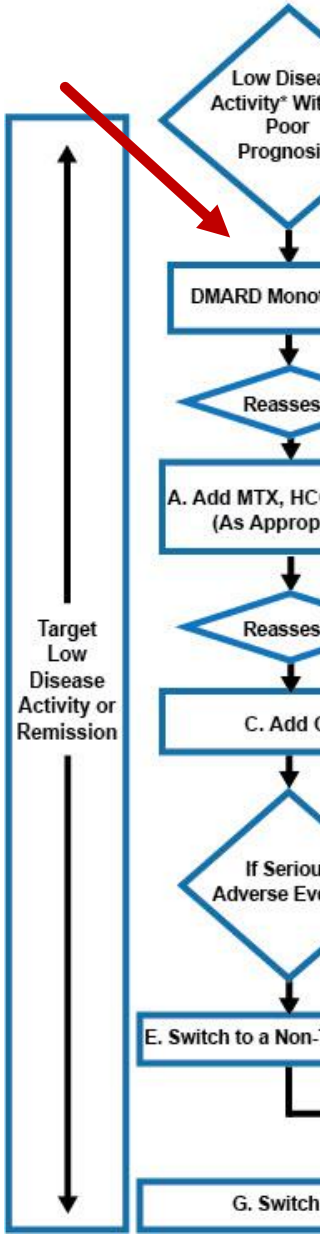
Disease and management beliefs of elderly patients with rheumatoid arthritis and comorbidity: a qualitative study

The majority of patients shared beliefs about the etiology of their RA and/or comorbidity. These patients attributed their day-to-day physical complaints or comorbidity to RA or to the medication prescribed for RA. These assumptions were sometimes correct (e.g., steroid-induced diabetes mellitus or hypertension due to leflunomide), but in some cases, the link between the complaint/comorbidity and RA was less clear (e.g., blurry vision due to methotrexate). Prednisone often appeared to be "the malefactor" (quote 12). Participants expressed that side effects did not affect their medication adherence.

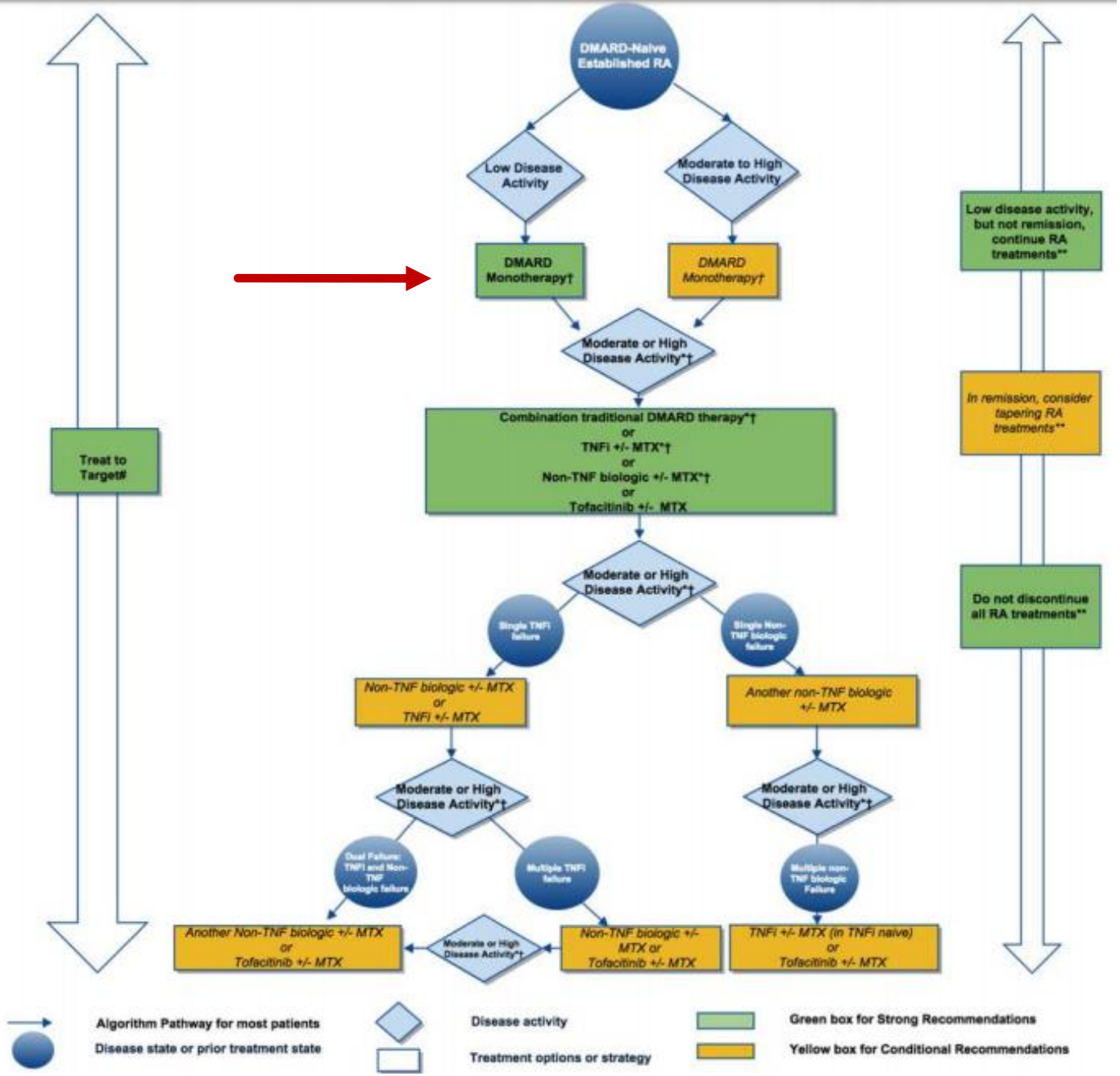
Quote 12: "I still think that prednisone is the malefactor. I just do not want it. Yes prednisone, you get a moonface. You feel very unhappy." *Patient 1, 67 years old.*

Quote 13: "First I used naproxen with methotrexate. At the pharmacy, they told me that naproxen is not good for my heart. I told this to my rheumatologist and I had to make a choice. And I honestly chose for my heart." *Patient 2, 60 years old.*

Patients in our study prioritized their conditions but expressed to be equally adherent for the medication prescribed for chronic conditions that they perceive as less important. This finding is in contrast to the findings of Rifkin et al., where participants tended to prioritize their medication based on their perceived importance of the condition [14]. Only when RA medication had to be changed due to another condition, the majority of the participants in our study preferred the treatment of the comorbidity. Furthermore, about half of the patients explicitly expressed that it is important to take as few medications as possible, sometimes even at the cost of higher disease activity. Similar perspectives were found in a qualita-



The 2012 ACR Tr



2015 ACR Guideline for the Treatment of Rheumatoid Arthritis

Guidelines for the Use of Conventional and Newer Disease-Modifying Antirheumatic Drugs in Elderly Patients with Rheumatoid Arthritis

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- Responsabilità del clinico
- Fattori legati all'età
- Efficacia
- Rischio tossicità, posologia

optimal treatment. Although the reasons for this have not been completely defined, it seems clinicians are reluctant to use DMARDs in the elderly because of uncertainty regarding their efficacy and safety in this population. The aging process is associated with important changes in drug pharmacokinetics and pharmacodynamics. It appears that the former, mainly through decreased renal clearance, is responsible for an increased incidence of adverse effects with some DMARDs. The old are also more susceptible to infection than the young, making prevention of infectious disease through vaccination of particular importance; however, healthcare professionals should be aware that some DMARDs, including biologic agents, may interfere with responses to vaccination. The available data, although limited, suggest that DMARDs, including some biologic agents, are similarly effective in the old and the young, while maintaining very good adverse effect profiles. Therefore, the elderly with RA should not be excluded from receiving optimal treatment with these medications. At the same time, clinicians must be aware of the possible increased risk of drug toxicities, recognize the need to adjust therapy to match individual patient characteristics (i.e. renal function, co-morbidities, concomitant medication use or polypharmacy), and use the lowest possible effective dosage. This review

Diaz-Borjon A , 2009

METHOTREXATE

- Derivato dell'aminopterina, ag anti-leucemico
- antimetabolita che previene produzione di purine e pirimidine attraverso l'inibizione della diidrofolato reduttasi
- promozione di rilascio di adenosina mediante inibizione dell'amminoimmidazolecarbossammido ribonucleotide trasformilasi → ridotta sintesi di citochine proinfiamamtorie (TNF, IL-6); incremento IL-10
- Primo utilizzo in RA 1950
- Studi clinici 1980
- Gold standard

VANTAGGI:

- Più rapido di altri DMARDs (1-2 mesi)
- Rallenta processo erosivo
- Riduzione mortalità

Alarcon GS, et al, 1992; Cronstein BN et al, 1992

METHOTREXATE

- Metabolizzato dal fegato in metaboliti attivi che rimangono nei tessuti per periodi di tempo prolungati e possono essere riconvertiti in MTX
- Emivita terminale di 3-10 ore
- Eliminazione prevalentemente per escrezione renale e il resto biliare.

OVER 60

- diminuzione significativa della sua eliminazione correlata a diminuita clearance
- Interruzione: a.e. piuttosto che inefficacia
- Efficacia sovrapponibile
- Dosaggi ridotti

J Rheumatol 1995;
Wolfe F, et al 1991;
Bologna C, et 1996;
Bressolle F et al, 1997*;*
Sandoval DM et al,1995;
Alarcon GS et al, 1995

Do patients with older-onset rheumatoid arthritis receive less aggressive treatment?

Z Tutuncu, G Reed, J Kremer, A Kavanaugh

Ann Rheum Dis 2006;**65**:1226–1229. doi: 10.1136/ard.2005.051144

Table 1 Characteristics

Age (years)
Weight (lbs)
Duration of RA (years)
Disability Index
DAS28
TJS
SJS
PhGA
Patient VAS general
Patient VAS for pain

DAS, Disease Activity Score; P
Score; TJS, Tender Joint Score

Table 2 Characteristics of patients by comorbidities

	Age at onset of RA						
	⩾60 years			40–60 years			
	%	Freq	n	%	Freq	n	p Value
Sex (female)	69.3	1440	2077	71.9	1506	2094	0.072
Use of methotrexate	63.9	1342	2101	59.6	1253	2101	0.005
Use of biological agent	23.0	323	2101	33.1	696	2101	0.000
Use of >1 DMARD	30.9	649	2101	40.5	851	2101	0.000
Use of prednisone	41.0	837	2039	37.64	778	2067	0.025
Hx of peptic ulcer disease	6.4	135	2101	5.6	118	2101	0.299
Hx of CAD	8.9	187	2101	3.7	77	2101	0.000
Hx of GERD	16.8	353	2101	16.7	352	2101	1.000
Hx of MI	5.9	125	2101	3.0	63	2101	0.000
Hx of hypertension	41.4	870	2101	27.4	575	2101	0.000
Hx of stroke	3.8	79	2101	1.4	30	2101	0.000
Hx of CVD*	14.4	303	2101	6.6	138	2101	0.000

CAD, coronary artery disease; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drug; Freq, frequency; GERD, gastroesophageal reflux disease; Hx, history; MI, myocardial infarction; RA, rheumatoid arthritis.
*CAD, MI, stroke combined.

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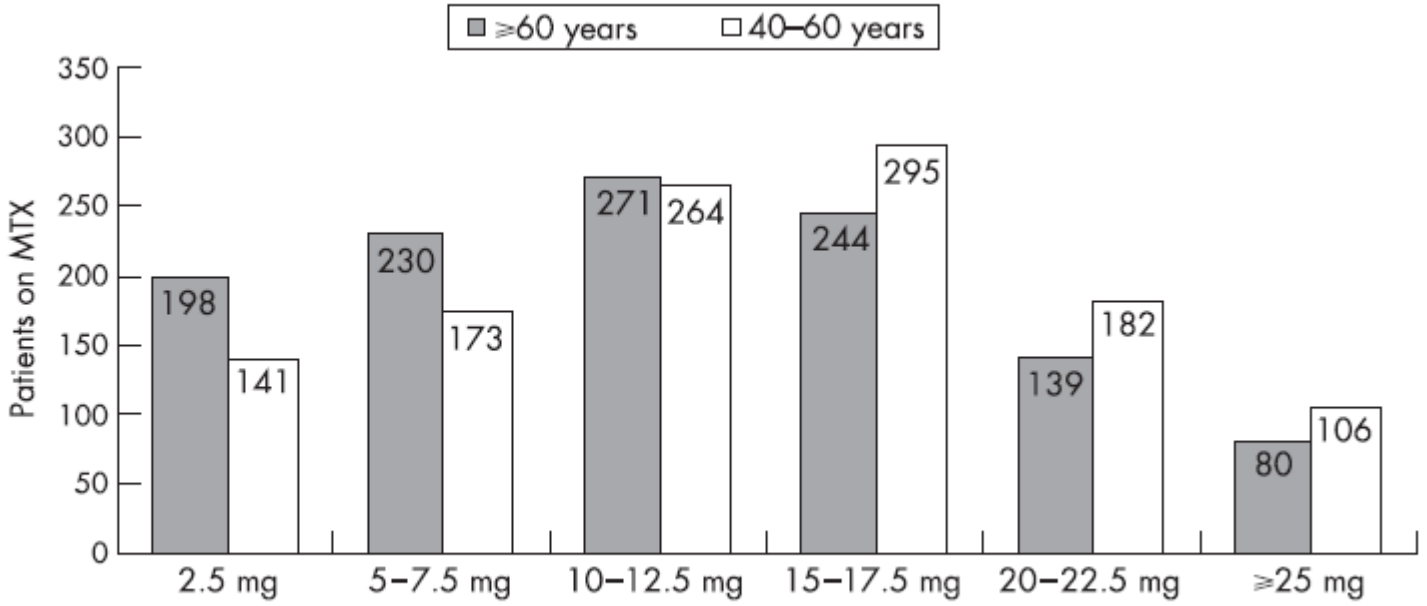

Figure 1 Distribution of methotrexate (MTX) dose.

Do patients with older-onset rheumatoid arthritis receive less aggressive treatment?

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regression analyses. Estimates of differences in methotrexate dose were made using a random effects model with duration of disease as the random effect (thus clustering on duration of disease). ORs for risks of toxicities were estimated using random effects logistic regression with duration and patient (nested in the duration group) as random effects.

RESULTS

Comorbidities were more common among the EORA group than among the YORA group: coronary artery disease: 8.9% *v* 3.7%; myocardial infarction: 5.9% *v* 3.0%; hypertension: 41.1% *v* 27.4%; stroke: 3.8% *v* 1.4%, respectively. Interestingly, patients with YORA were heavier than those with EORA (mean: 182.3 *v* 164.6 lbs, respectively). Scores for several measures, such as the HAQ DI, TJC, PGA and PPA, were higher among patients with YORA, whereas the DAS28 and SJC were comparable (table 2).

The use of methotrexate was more common in patients with EORA (63.9% *v* 59.6%; $p<0.01$). However, the percentage of patients with EORA who were on multiple DMARD treatment (30.9%) or on biological agents (25%) was markedly lower than those with YORA (40.5% and 33.1%, respectively; $p<0.0001$). The use of prednisone was slightly higher among patients with EORA (41%) than among those with YORA (37.64%; $p<0.05$; table 2).

Predictors of the use of methotrexate, multiple DMARD and biological treatments were estimated using conditional logistic regression analysis. EORA, low HAQ DI, TJC, SJC and PGA correlated with use of methotrexate, whereas YORA, high HAQ DI, high DAS28, TJC, SJC, PhGA score, PGA score and use of prednisone correlated with biological usage. YORA, high HAQ DI, DAS28, TJC, SJC, PGA and use of prednisone correlated with use of multiple DMARDs. Among the comorbidities investigated in this study population, only history of hypertension was a negative predictor of the use of biological agents and multiple DMARDs. The presence of other comorbidities did not seem to have an influence on the choice of therapeutic agents.

Although methotrexate was more commonly used by patients with EORA, the weekly methotrexate dose was considerably lower among them (mean = 11.96 mg, median = 11.25 mg) than in those with YORA (mean = 13.53 mg, median = 16.25 mg). Methotrexate dose also correlated with weight, TJC and use of prednisone. The distribution of methotrexate dose among patients with YORA and EORA is shown in fig 1.

METHOTREXATE

- Nessun effetto su demineralizzazione ossea da solo
- Effetto potenziante su decalcificazione indotta da corticosteroidi

Nell'anziano:

- insufficienza renale lieve
- sintomi di tossicità del SNC: alterazione dell'umore, disturbi della memoria e sensazione di confusione mentale

Buckley LM et al, 1997

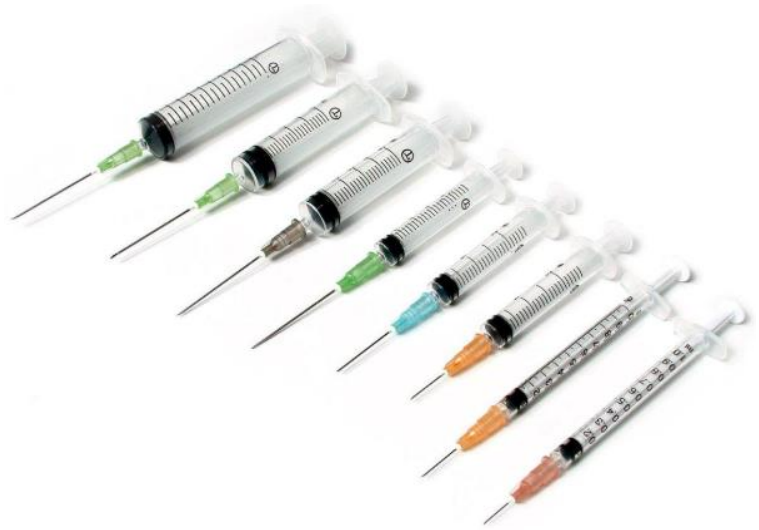
METHOTREXATE

Table I. Toxic and adverse effects of methotrexate, and guidelines for monitoring its use in patients with rheumatoid arthritis

System/organ	Adverse/toxic effect	Baseline evaluation	Monitoring
Gastrointestinal (most common)	Oral ulcers, nausea, vomiting, abdominal pain/discomfort, diarrhoea, hepatotoxicity	Chest x-ray, liver function tests (including albumin), blood urea nitrogen, creatinine, complete blood count (including platelet count) and hepatitis B and C serology	Complete blood count (including platelet count), liver function tests (including albumin), blood urea nitrogen and creatinine every 4–8 weeks
Pulmonary	Interstitial pneumonitis, pulmonary nodulosis		
Haematological	Leukopenia, thrombocytopenia, megaloblastic anaemia, non-Hodgkin's lymphoma (Epstein-Barr virus-associated)		
Renal	Decreased creatinine clearance		
Skin	Nodulosis, alopecia		
Reproductive	Teratogenesis, oligospermia		
Metabolic	Hyperhomocysteinaemia		
Nervous system	Headache, neurotoxicity, seizures (very rare)		

METHOTREXATE

- Supplementazione di ac folico
- Riduzione posologica se IR



7.5 mg
10 mg
12.5 mg
15 mg
17. 5 mg
20 mg
25 mg

- Sicuro nell’anziano

ANTIMALARICI (CQ, HCQ)

- Primi anni ’50
- Az stabilizzante sui lisosomi → diminuzione della formazione MHC II necessario per le cellule presentanti l'antigene a stimolare i linfociti T CD4 +
- Sia idrossiclorochina che clorochina sono prontamente assorbiti nel tratto gastrointestinale, hanno un grande volume di distribuzione con predilezione per i tessuti pigmentati (pelle e retina).
- Parzialmente metabolizzati dal fegato.
- Lunghe emivite (1-2 mesi).
- La forma primaria di eliminazione è attraverso le urine.

Adams EM et al 1983
Clark P et al, 1993
Jessop JD et al, 1998
Davis MJ et al, 1991
Avina-Zubieta JA et al, 1998
Fox RI et al, 1993

ANTIMALARICI

- L'efficacia per il trattamento della RA è stata dimostrata in studi retrospettivi e studi clinici
- L'idrossiclorochina sembra avere leggermente meno efficacia e meno tossicità rispetto alla clorochina.
- Azione lenta (3-6 mesi)
- No azione su progressione radiografica
- Efficacia globale inferiore
- Effetto additivo in combinazione (in particolare MTX)
- Riservata ad artrite lieve e non erosiva
- Ben tollerati

O'Dell JR et al, 1996
Trnavsky K et al,1993

ANTIMALARICI

- Tossicità oculare eccezionale i dosaggi rccomandati (<3 mg /kg /die per la CQ e <6,5 mg /kg /die per HCQ)

Fattori di rischio predisponenti:

- alterata funzione renale o epatica
- aumento del grasso corporeo
- cheratopatia preesistente
- Età > 60 anni
- Durata del trattamento> 5 anni.

Dato l'aumentato rischio di degenerazione maculare senile negli anziani indicato follow-up

Marmor MF et al, 2002
Bernstein HN, 1991
Mackenzie AH, 1983
Araiza-Casillas et al, 2004

ANTIMALARICI

Table II. Toxic and adverse effects of antimalarials, and guidelines for monitoring their use in patients with rheumatoid arthritis

System/organ	Adverse/toxic effect	Baseline evaluation	Monitoring
Eye (rare)	Retinal toxicity, corneal deposits	Ophthalmological examination if age >40 years or pre-existing eye disease, liver function tests and creatinine	Ophthalmological evaluation yearly
Gastrointestinal (most common)	Nausea/vomiting, abdominal pain, diarrhoea		
Neuromuscular (rare)	Myopathy		
Haematological (rare)	Aplastic anaemia, agranulocytosis, thrombocytopenia		
Skin	Pigmentation of skin and mucosa (very long-term use), hair bleaching, pruritus		
Cardiovascular (rare)	Cardiomyopathy, heart block		
Nervous system	Headache and dizziness (common), ototoxicity, seizures (very rare)		

SULFASALAZINA

- Primo farmaco studiato specificatamente per la RA fine aa ‘40, dati contrastanti
- Reintrodotto come antiartritico a partire dagli anni ’70
- Composta da due molecole, la sulfapiridina e l’acido 5-aminosalicilico
- Nell'intestino crasso i batteri riducono la sulfasalazina a sulfapiridina e 5-ASA; la maggior parte della sulfapiridina viene assorbita nel colon, mentre il 5-ASA è quasi completamente escreto nelle feci
- Nausea e vomito negli acetilatori lenti
- Eliminazione renale

Pullar T et al, 1985
Bird HA et al,1995
Morabito L et al, 1998

SULFASALAZINA

- Inibizione della PGE e sintesi di leucotrieni, riduzione Ig e fattore reumatoide, inibizione della funzione dei neutrofili e dei linfociti, riduzione della proliferazione dei linfociti T e B, riduzione di IL-1, IL-6, IL-12 e TNFa.
- Capacità di rallentare la progressione radiografica in diversi studi randomizzati osservazionali.
- Efficacia paragonabile a quella di MTX, LEF, sali d'oro iniettabili e penicillamina.
- Inizio di azione più rapido rispetto all'idrossiclorochina.

Wilkieson CA et l,1993
Dougados Met al, 1999

SULFASALAZINA

- Terapia combinata di SSZ+MTX ha mostrato modeste differenze rispetto alla monoterapia
- La combinazione di SSZ+MTX+HCQ efficacia significativamente migliore rispetto a qualsiasi di questi agenti usati in monoterapia, alla SSZ+MTX e lievemente superiore a MTX+HCQ.
- Efficacia paragonabile in giovani e anziani
- Studi di farmacocinetica della sulfasalazina negli anziani hanno concluso che vi è un'emivita di eliminazione prolungata.
- Nessuna differenza frequenza o natura degli effetti avversi.

Sinclair RJG, et al,1949
Taggart AJ et al, 1987
Svartz N, 1988
McConkey B et al, 1980
van der Heijde DM, et al, 1989

Nuver-Zwart IH et al, 1989
Calguner M et al, 1999
Gubae EE et al, 2008
O'Dell JR et al, 2002

SULFASALAZINA

Table III. Toxic and adverse effects of sulfasalazine, and guidelines for monitoring its use in patients with rheumatoid arthritis

System/organ	Adverse/toxic effect	Baseline evaluation	Monitoring
Gastrointestinal (most common)	Nausea/vomiting, dyspepsia, diarrhoea, hepatotoxicity (rare)	Complete blood count, liver function tests, blood urea nitrogen, creatinine, and consider glucose-6-phosphate dehydrogenase levels	Complete blood count, liver function tests, blood urea nitrogen and creatinine every 2–4 weeks for 3 months, then every 3 months
Skin	Rash, photosensitivity, pruritus		
Systemic	Fever		
Haematological (rare)	Haemolytic anaemia (in glucose-6-phosphate dehydrogenase deficiency), aplastic anaemia, agranulocytosis		
Renal	Nephrotoxicity, crystalluria, haematuria		
Nervous system	Headache, anorexia		
Reproductive	Oligospermia		

LEFLUNOMIDE

- Farmaco studiato specificatamente per la RA aa ’80
- Derivato isossazolico che esercita inibizione di diidroorato deidrogenasi, quindi previene la produzione de novo di pirimidina necessaria per la sintesi del DNA.
- Diminuzione della proliferazione e differenziazione dei linfociti T
- Inibizione della trascrizione di nf-kB, attività cicloossigenasi-2 e metalloproteinasi
- Aumento TGF-beta

Bartlett RR et al,1985

LEFLUNOMIDE

- Buona biodisponibilità x os ed è rapidamente metabolizzato nel suo metabolita attivo, A77 1726, che si lega quasi completamente alle proteine plasmatiche
- È metabolizzata dal fegato, in parte eliminata nella bile, con significativo circolazione enteroepatica; il resto viene eliminato per via renale.
- Emivita di circa 2 settimane; metaboliti attivi possono essere rilevati fino a 2 anni dopo che il trattamento si è interrotto a causa del ricircolo biliare

LEFLUNOMIDE

- Efficacia paragonabile a quella di SSZ e MTX
- Terapia combinata di LEF e MTX si è dimostrata sicura ed efficace nei pazienti con risposta insufficiente al solo MTX
- Questa combinazione non è stata studiata negli anziani.

Mladenovic V et al, 1995
Strand V et al, 1999
Emery P et al, 2000
Cohen S et al, 2001
Smolen JS et al, 1999
Strand V et al, 1999
Kremer JM et al, 2002
Yao Y et al ,2013

LEFLUNOMIDE

- Non vi sono studi sugli anziani
- Gli esperti consigliano il dosaggio ridotto di 20 mg a dì alterni
- Casi di maggior rischio di pancitopenia negli anziani (in particolare in associazione a MTX)
- Ipertensione arteriosa (nuova insorgenza o esacerbazione) è un effetto avverso comune che va considerato in particolare in pz anziani con co-morbidità come insufficienza cardiaca, IRC
- Colestiramina (8 g/x3/die x 11 gg)

Olivieri I et al, 2005
Chan J et al, 2004

LEFLUNOMIDE

Table IV. Toxic and adverse effects of leflunomide, and guidelines for monitoring its use in patients with rheumatoid arthritis

System/organ	Adverse/toxic effect	Baseline evaluation	Monitoring
Gastrointestinal (most common)	Diarrhoea, nausea, abdominal pain, hepatotoxicity	Complete blood count, liver function tests (including albumin) and hepatitis B and C serology	Complete blood count and liver function tests (including albumin) every 4–8 weeks, BP monitoring at every visit
Cardiovascular	Hypertension (new onset or exacerbation)		
Skin	Alopecia, rash		
Nervous system	Anorexia, headache, peripheral neuropathy		
Haematological (rare)	Agranulocytosis, thrombo-cytopenia, pancytopenia		
Pulmonary (very rare)	Interstitial pneumonitis		

BP = blood pressure.

SALI D'ORO

- prima parte del 20 ° secolo
- Meccanismo d'azione sconosciuto
- Formulazione orale e parenterale (più efficace)
- L'oro per via parenterale si dimostrato efficace in più studi, anche rispetto ad altri DMARD
- Prevengono le erosioni articolari
- studio in doppio cieco, controllato con placebo, l'auranofina è risultata sicura ed efficace in pazienti con EORA con effetto di risparmio di corticosteroidi

Ward JR et al, 1983
Jessop JD et al, 1998
Glennas A et al, 1997

SALI D'ORO

- Le reazioni avverse gravi sono rare ma possono essere fatali.
- La reazione nitritoide associata all'oro i.m. è caratterizzata da reazioni vasomotorie, diaforesi, ipotensione, nausea, vomito e sincope, che possono essere di particolare preoccupazione nei pazienti anziani.
- Nei pz anziani associazione tra questo e.c. e l'uso di ACE-inibitori
- Tp obsoleta

Bluhm GB et al, 1982
Lorber A et al 1982
Nixon J et al 2006

CICLOSPORINA

- Efficace nel trattamento della RA
- Si è dimostrata in grado di rallentare la progressione radiografica.
- La combinazione con metotrexato è sicura ed efficace nei pazienti con RA grave che non rispondono in modo soddisfacente al metotrexato
- Il meccanismo d'azione RA sembra essere correlato al suo effetto immunosoppressivo sulle cellule T
- La farmacocinetica è influenzata dall'età e risente della politerapia pertanto sono raccomandati dosaggi più bassi negli anziani
- Uso limitato principalmente a causa del suo alto costo e del profilo di tossicità, in particolare nefrotossicità e ipertensione

Jones G et al, 2003 ; Pasero G et al, 1996 ; Tugwell P et al,1995 ; Kovarik JM et al, 1999; Gremese E et al, 2004

AZATIOPRINA

- Analogo purinico che inibisce la sintesi del DNA con proprietà immunosoppressive sui linfociti
- Prove a supporto dell'efficacia dell'AZA in RA derivate principalmente da studi con piccolo numero di soggetti.
- Efficacia inferiore a MTX
- Tossicità da AZA più elevata e più seria di quello di altri DMARD
- Può essere utile nei pazienti con vasculite sistemica associato con RA.
- Non ci sono studi che affrontano l'uso di questo farmaco negli anziani
- L'utilizzo nei pz anziani dovrebbe essere intrapreso con cautela.
- Significativo numero di interazioni, es. allopurinolo

Kovarik JM et al, 1999; Gremese E et al, 2004; Suarez-Almazor ME et al,2000; Jeurissen MEet al,1991; Heurkens AH et al, 1991; Elion GB. et al,1993; Kennedy DT et al, 1996

ALTRI DMARDS

Table V. Toxic and adverse effects of other conventional (synthetic) disease-modifying antirheumatic drugs (DMARDs), and guidelines for monitoring use of these drugs in patients with rheumatoid arthritis

DMARD	Adverse/toxic effect	Baseline evaluation	Monitoring
Gold salts (intramuscular)	Stomatitis, rash, nitritoid reactions, nausea, vomiting, hepatotoxicity, myelosuppression, nephrotoxicity, pneumonitis	CBC[a], BUN, creatinine and urinalysis; consider LFTs	CBC[a] and urinalysis every 2 weeks while on weekly injections, then with each injection; consider LFTs, BUN and creatinine every 3 months
Auranofin (oral gold)	Nausea, vomiting, abdominal pain, diarrhoea rash, stomatitis, dysgeusia, hepatotoxicity, pneumonitis, nephrotoxicity, myelosuppression	CBC[a], BUN, creatinine, LFTs and urinalysis	CBC[a], BUN, creatinine, LFTs and urinalysis every 4–8 weeks
Penicillamine	Myelosuppression, pneumonitis, nephrotoxicity, hepatotoxicity, SLE-like syndrome	CBC[a], urinalysis, BUN and creatinine; consider LFTs	CBC[a] and urinalysis every 2 weeks for 6 months, then every month; consider BUN, creatinine and LFTs every 1–3 months
Minocycline	Nausea, vomiting, diarrhoea, abdominal discomfort, dizziness, vertigo, headache, skin hyperpigmentation, cytopenias, hepatotoxicity (rare)	CBC[a], BUN, creatinine and LFTs	No specific recommendations; consider CBC[a] and LFTs periodically
Ciclosporin	Hypertension, nausea, vomiting, hirsutism, headache, nephrotoxicity, hepatotoxicity, hyperglycaemia, dyslipidaemia, hyperuricaemia (and gout), electrolyte abnormalities, cytopenias, anaemia	BP, CBC[a], BUN, creatinine, LFTs and uric acid	BP at every visit; BUN and creatinine every 2 weeks until dose stable, then every month; CBC[a], LFTs and electrolytes (potassium) periodically. Consider lipid panel
Azathioprine	Nausea, vomiting (treatment limiting), myelosuppression, hepatotoxicity, hypersensitivity, malignancy (including lymphoma)	CBC[a], BUN, creatinine and LFTs; consider TPMT genotyping/ phenotyping	CBC[a] every 1–2 weeks with dose changes, then every 1–3 months along with LFTs

a Including platelet count.

BP = blood pressure; **BUN** = blood urea nitrogen; **CBC** = complete blood count; **LFTs** = liver function tests; **SLE** = systemic lupus erythematosus; **TPMT** = thiopurine methyltransferase.

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arthritis research&therapy

RESEARCH ARTICLE Open Access

DMARD non-use in low-income, elderly rheumatoid arthritis patients: results of 86 structured interviews

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Età media 80 aa
Durata media di mal 25 aa

Disease-modifying antirheumatic drugs (DMARDs) have been recommended as the standard of care because of their consistent reduction of pain and disability in patients that have lived RA for several decades [7]. Studies demonstrate that delays in the implementation of DMARD treatment have been associated with increased physical disability, radiologic damage, and other long-term health outcomes [8,9]. As a result, the American College of Rheumatology (ACR) and European League Against Rheumatism both recommend early and aggressive DMARD treatment to essentially all patients with RA [10,11].

Despite these recommendations, DMARD treatment rates among RA patients are suboptimal. Investigators

iveness Data and Information Set data demonstrated that only 63% of RA patients used DMARDs, and use was 30% less likely among patients older than 85 years [12]. Several other insurance claims-based studies have confirmed that increasing age may act as a deterrent for using DMARDs [13-15]. Low-socioeconomic status and lack of rheumatic disease specialty care have also been identified as predictors of suboptimal DMARD use in populations, after adjusting for health care and drug-insurance benefits [15,16].

Table 3 Attitudes and knowledge of DMARDs among 65 never-users

	Never-users
What are some reasons you never started DMARDs?	
Never heard of DMARDs	17 (26.2%)
Never been offered DMARDs	35 (53.8%)
Do not need DMARDs	10 (15.4%)
Afraid of DMARRD side effects	13 (20.0%)
Taking too many other medications	8 (12.3%)
Do not see physicians often	1 (1.5%)
Other medical problems take precedence	2 (3.1%)
Inconvenience	1 (1.5%)
What are some reasons you would use a DMARD?	
Stops joint damage	1 (1.5%)
Relieves pain or swelling	12 (18.5%)
Physician recommendation	8 (12.3%)
If rheumatoid arthritis worsens	1 (1.5%)
If the DMARD has no side effects	1 (1.5%)
Have you ever talked to a physician about any DMARDs?	
Yes	9 (13.8%)
No	56 (86.2%)
Have you ever looked up information about DMARDs?	
Yes	1 (1.5%)
No	64 (98.5%)
Do you know anything about DMARDs in general?	
Side effects	11 (16.9%)
Benefits	1 (1.5%)
Method of administration	1 (1.5%)
Nothing	53 (81.5%)
Total missing	2

Of the 67 never-users, 65 answered these questions.

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Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients

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No correlations of age with changes in SDAI and HAQ-DI were seen in the MTX group ($r = 0.07$ and 0.05, respectively;

Radiographic progression was independent of age

old. The efficacy of treatment response in all age groups is comparable and slight numerical differences appear to be clinically meaningless. Drop-out rates or patients lost to follow-up

cally meaningless. Drop-out rates or patients lost to follow-up during 1 year of treatment were low (~13%) and similar in all age groups, indicating that patients in the highest quartile were not more prone to premature discontinuation of study drugs than younger individuals. The known superiority of a combination

younger individuals. The known superiority of a combination therapy with TNFi + MTX to that of MTX monotherapy has been observed in all studied subgroups, also independent of age.

Alternative a MTX nell'anziano

THERAPY IN PRACTICE

Drugs Aging 2003; 20 (10): 723-736
1170-229X/03/0010-0723/$30.00/0

Methotrexate Intolerance in Elderly Patients with Rheumatoid Arthritis

What Are the Alternatives?

Alexandros A. Drosos

Table IV. Suggested therapeutic approach for elderly rheumatoid arthritis patients intolerant of methotrexate

Disease severity	Treatment approach
Mild to moderate	Small doses of corticosteroids (example: prednisone 7.5 mg/day) + hydroxychloroquine or sulfasalazine
Moderate to severe	Small doses of corticosteroids, as above + cyclosporin or leflunomide
Severe disease and when other DMARDs are contraindicated	Small doses of corticosteroids as above + anticytokine therapy

DMARDs = disease-modifying antirheumatic drugs.

OBIETTIVI

YORA	EORA
•Tp aggressiva ab initio •Mantenere la funzionalità a lungo termine •Riduzione dei sintomi •Riduzione disabilità e perdita giorni lavorativi •Qualità della vita e relazioni sociali	•Minima dose efficace •Mantenere funzionalità e indipendenza nel breve termine •Ridurre il dolore •Attenzione a comorbidità e poli-tp •Attenzione alle infezioni

Rheumatoid arthritis: appropriate treatment in older people

Gayle McKellar MRCP

Drug	Specific cautions in older people
NSAIDs	gastric complications renal dysfunction higher risk CNS side-effects
Paracetamol	nil if liver function normal
Opioids	higher risk CNS side-effects and constipation – consider avoiding
Oral steroids	diabetes cardiovascular side-effects weight gain GI side-effects osteoporosis
Methotrexate	monitor liver and renal function higher risk of bone marrow toxicity
*Leflunomide**	monitor LFTs and BP
Sulfasalazine	GI side-effects problems with administration of large pills
Gold	higher risk renal toxicity
Hydroxychloroquine	retinal toxicity risk no higher than in younger population
Combination DMARD therapy	strict monitoring as recommended for any patient
Anti-TNF therapy	similar rates of malignancy and infection as in younger patients
*consider omitting loading dose in older people	

Grazie