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Review

Management of inflammatory rheumatic conditions in the elderly

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Abstract

The number of elderly people with chronic inflammatory rheumatic diseases is increasing. This heterogeneous and comorbid population is at particular risk of cardiovascular, neoplastic, infectious and iatrogenic complications. The development of biotherapies has paved the way for innovative therapeutic strategies, which are associated with toxicities. In this review, we have focused on the scientific and therapeutic changes impacting the management of elderly patients affected by RA, SpA or PsA. A multidimensional health assessment resulting in an integrated therapeutic strategy was identified as a major research direction for improving the management of elderly patients.

Key words: elderly, biotherapies, inflammatory rheumatism, efficacy, safety, management

REVIEW

Rheumatology key messages

- Elderly inflammatory rheumatic disease patients should be provided with individualized care.
- A multimodal evaluation could improve the quality of care for elderly IRD patients.
- Studies of elderly care are necessary to develop specific recommendations in IRD.

Introduction

As a result of increasing life expectancy, risk transition and improved quality of care, the number of people living with at least one chronic disease is increasing [1]. Chronic inflammatory rheumatic diseases (IRDs) affect 2–3% of the general population, involving a non-negligible proportion of elderly subjects. Almost one-third of RA patients are >60 years of age, and elderly patients with IRDs are at particular risk for cardiovascular, neoplastic and infectious complications. Furthermore, IRD in the elderly may have a distinct clinical and biological presentation, with differing responses to treatment.

These features reflect the physiological changes (e.g. immunosenescence and alterations in pharmacokinetics) and comorbidities (diabetes, obesity, renal failure, etc.) associated with ageing, which vary widely from one individual to another [2, 3]. Multimorbidity and polypharmacy, both of which are common in the elderly, are well-known risk factors for adverse drug reactions (ADRs) and interactions [4].

In parallel with this epidemiological evolution, a new class of maintenance therapy agents known as biologics, which comprise specific antibodies with immunomodulating properties, has emerged, thereby expanding the therapeutic arsenal hitherto containing DMARDs, such as MTX, and anti-inflammatory drugs.

Paradoxically, elderly patients have mostly been left out of new therapeutic opportunities. Randomized controlled trials and prospective cohorts primarily recruit healthy or single-disease volunteers rather than elderly and comorbid patients [5]. Thus, the extrapolation of findings to real-life elderly patients may be compromised. Against this background, the novel mechanisms of action of biologics and paucity of literature specifically pertaining to the elderly have raised concerns about the safety of these new drugs, leading to more conventional therapeutic regimens in this population.

Hypothesis and search strategy

Several hypotheses guided our study: biologic treatments could benefit both older and younger people; physiological and pathological ageing associated with comorbidities, as well as co-treatment, could partly explain the risk of serious adverse events (AEs) (e.g. infection, cancer,

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neoplasia, fractures) observed with treatment; and beyond the specific treatments (DMARDs), a more global care strategy could improve outcomes, such as health related quality of life (HR-QoL) and autonomy.

We searched PubMed's MEDLINE and the Web of Science database for studies published over the past 10 years. The search ended in October 2017. Keywords elderly, ageing, aged, recommendations or guidelines were combined with RA, SpA or PsA. The search was limited to articles published in English. The reference lists of relevant articles and conference proceedings were searched manually.

In this overview, we focus on the therapeutic progress impacting the management of elderly with RA, spondyloarthropathy (SP) and PsA, highlighting gaps in the literature concerning this growing, but under-studied, population

RA

Specificities of initial presentation in the elderly

Most studies refer to older subjects without specifying whether the disease appeared after 60 years of age (elderly-onset RA, EORA) or at a younger age (young-onset RA, YORA). For this overview, the term EORA will be reserved for studies specifying an old age of onset. EORA has specific clinical and biological characteristics. The female predominance is less marked, disease onset more abrupt, morning stiffness prolonged and constitutional symptoms more severe than in YORA [6]. The differential diagnosis with PMR or microcrystalline arthritis is more challenging due to common proximal joint involvement [7]. EORA is associated with increased MRI-detected inflammation, but this effect of age is similar in controls, supporting the hypothesis of a general and non-disease-specific effect of age on MRI inflammation, possibly related to immunosenescence [8].

Higher IL-6 and lower TNFα levels have been observed in EORA compared with YORA [9]. In the elderly population, high levels of TNFα are associated with an increased risk of hospitalization and death at 1 year [10]. EORA patients often present with higher DAS 28 and Ratingen scores at diagnosis [11], increased inflammation and disability [12–14] and a greater number of comorbidities [12], but less RF and ACPA positivity [15].

Age and treatment effectiveness

Due to the lack of specific studies in the elderly, conventional synthetic DMARDs (csDMARDs) in combination with glucocorticoids (GCs) constitute the initial treatment for RA, as in younger subjects [16, 17]. As the reference csDMARD, MTX remains the gold standard in EORA management. The rare studies investigating its efficacy in the elderly have not revealed decreased effectiveness of csDMARDs compared with YORA. Pooled data from 11 MTX clinical trials involving 496 RA patients revealed no effect of age or renal impairment on MTX efficacy [18]. In the Swedish Farmacotherapy (SWEFOT) trial, higher age was associated with an increased likelihood of EULAR response to MTX in patients with new-onset RA [19]. A retrospective series of 90 RA patients showed no impact of age on the efficacy of LEF [20]. Despite widespread use of GCs, particularly in elderly RA patients [21], initial dosage, optimal treatment duration, tapering strategies and the timing and frequency of administration remain largely empirical [22]. Expert reports advocate as low a dose and as short a duration as possible, *a fortiori* in elderly and fragile subjects [17].

Numerous studies have documented the effectiveness of biotherapies (mainly TNFα inhibitors, TNFi) in EORA (Table 1). In several registries, TNFi were found to be slightly less effective in patients aged >65 years in terms of improvements in disease activity [23–25], radiographic damage [15], functional recovery [26] and HR-QoL [27]. However, some registries have shown no effect of age on the response to TNFi [28] or radiological progression after 5 years of treatment [11]. Moreover, randomized controlled trials have demonstrated that the benefits in terms of clinical response and radiographic progression when adding etanercept (ETA) [29, 30], infliximab or adalimumab [31] to MTX for RA treatment are maintained in the elderly population compared with subjects aged <65 years. In a *post hoc* study of the open-label period of three studies concerning ETA in RA, there were no substantial differences in efficacy for ETN patients $\geqslant 65$ *vs* <65 years [32].

Data on other biologics are scarce and inconsistent. Regarding rituximab, a prospective study found no effect of age on changes in DAS 28 at 8 months [33], whereas in the French registry, patients aged >75 years were less likely to be good responders at 1 year [34]. Sekiguchi *et al.* [14] revealed no difference between YORA and EORA in achieving remission with abatacept as the initial DMARD, yet the functional remission rate was lower in elderly patients. These data are consistent with the Japanese and French registries, in which there was no age-related difference in effectiveness, respectively, 1 and 2 years after introducing abatacept [35, 36]. Matsuda *et al*. showed as much benefit of abatacept in the elderly as in the younger patients regarding HR-QoL, disease activity and reduction of GC dose [37]. A retrospective study assessing tocilizumab in RA patients found a significantly decreased number of elderly patients with good EULAR response and remission at 6 months [38]. Concerning oral Janus kinase inhibitors, patients aged >65 years had similar response rates to patients aged <65 years after 3 months of tofacitinib and baricitinib for moderate to severe RA in a pooled analysis of phase 3 trials [39, 40].

Age and adverse drug reactions

As both RA and ageing are associated with cardiovascular disease, malignancies, osteoporosis and infection, it may be difficult to determine the extent to which treatment is responsible for the occurrence of complications [41]. Older subjects are more susceptible to infectious complications, with most studies reporting a 2- to 3-fold higher risk of serious infections for those aged >65 years [42].

Table 1 The efficacy and safety of boDMARDs in elderly RA patients

References	Design	Efficacy	Tolerance
Bathon *et al.* [29]	Subset analysis (age ⩾65 years *vs* age <65 years) of four randomized controlled clinical studies ($n=1353$) or two long-term extensions ($n=1049$) studying ETA in DMARD-resistant or late stage RA	ERA tended to have somewhat less robust ACR responses to treatment than younger subjects. A similar slowing in radiographic progression after 1 year of ETA was observed in both age groups	Rates of SAE tended to be higher in ERA than YRA, but are equivalent to placebo- or MTX-treated ERA
Hyrich *et al.* [28]	Register of RA patients starting ETA ($n=1267$) or INF ($n=1612$). Mean age 55 (12) years	Age did not predict EULAR response or remission with either drug at 6 months	No assessment
Setoguchi *et al.* [58]	Cohort (mean age 70 years) comparing 1152 patients on boDMARDs with 7306 patients on MTX	No assessment	boDMARD patients showed no difference in haematological malignancies or solid tumour incidence compared with MTX users
Tutuncu *et al.* [59]	Register of 2101 patients with EORA (after 60 years of age) were matched on the basis of disease duration with 2101 patients with YORA (between 40 and 60 years of age)	No assessment	Toxicities related to treatment with ETA, INF, ADA, KIN or other DMARDs were similar in the EORA and YORA groups
Genevay *et al.* [23]	Longitudinal population-based cohort, including 1227 YRA <65 years of age and 344 ERA >65 years of age starting anti-TNF therapy (mean follow-up 22 months)	Mean change in DAS 28 scores at 2 years (−0.65 *vs* −0.58) was identical in ERA and YRA. HAQ score improved significantly less in ERA (−0.02) than in YRA (−0.1) due to the lack of improvement after 75 years of age	Drug discontinuation rates were identical in all age groups. Cancer was significantly more frequent in ERA than YRA (7.1 *vs* 0%; $P<0.05$)
Schneeweiss *et al.* [55]	Cohort of 15 597 RA patients initiating DMARD therapy (TNF antagonists: 469) >65 years of age (mean age 76.5 years)	No assessment	The rate of serious infections among initiators of anti-TNF therapy was equivalent to that of MTX initiators (RR = 1.0; 95% CI: 0.6, 1.7)
Askling *et al.* [60]	Cohort of 6366 RA patients starting anti-TNF therapy were compared with a biologics-naïve RA cohort ($n=61\,160$) regarding the medium-term risks of cancer (up to 6 years)	No assessment	No overall elevation of cancer risk was associated with TNF therapy, regardless of follow-up time or age (<50, 51–74, >75 years)
Köller *et al.* [31]	Pooled data from two randomized, controlled, double-blind trials including patients with early RA using ADA or INF + MTX (788) or MTX alone (448), classified by quartiles of age, with the highest age group comprising 61–82 years	After 1 year of MTX + TNF inhibitor therapy, improvement of a composite disease activity index, assessment of physical function and radiographic progression were similar across all age quartiles	No assessment
McDonald *et al.* [61]	Cohort of 20 357 veterans with RA, including 3661 patients treated with boDMARDs (mean age 59.3 years)	No assessment	Unlike use of anti-TNF, increased age was an independent risk factor for herpes zoster
Radovits *et al.* [62]	Register of 730 RA patients, categorized into three age groups (<45, 45–65 and >65 years) at initiation of anti-TNF. Longitudinal analysis of DAS 28 during the first year of treatment	Elderly patients had fewer EULAR good responses and remission and less improvement in disease activity and physical functioning than younger patients	Drug survival, co-medication use and tolerance were comparable between the three age groups
Filippini *et al.* [27]	Observational cohort including 1114 RA patients treated with	Decreases in DAS 28 and ESR were comparable, but the	Anti-TNFα therapy was discontinued by 42%

(continued)

TABLE 1 Continued

References	Design	Efficacy	Tolerance
	anti-TNF therapy (311 age ⩾65 years and 803 age <65 years) and followed up to 3 years	EULAR response was somewhat lower in the ERA. HAQ scores were higher at baseline with less improvement after treatment in ERA	of ERA and 36.6% of YRA SAEs, infection and overall cancer were higher among ERA
Hetland *et al.* [25]	Register of 2326 RA patients beginning boDMARDs (median age 57 years). Treatment responses were assessed after 6 and 12 months	Older age and initial low functional status were negative predictors of a clinical response and remission during anti-TNF treatment of RA	No assessment
Amari *et al.* [63]	Cohort of 20 648 veterans with RA (mean age 63 years), including 4088 patients treated with anti-TNFs	No assessment	Age (per decade, HR = 1.23; 95% CI: 1.09, 1.38) and anti-TNF use (compared with csDMARDs, HR = 1.42; 95% CI: 1.24, 1.63) were risk factors for developing NMSC
Galloway *et al.* [52]	Prospective observational study assessing the risk of severe infection between 11 798 and 3598 csDMARD-treated RA patients stratified by age (<55, 55–64, 65–74 and >75 years)	No assessment	The crude rate of infection increased markedly with age. The increased risk of SI associated with anti-TNF therapy (+20% compared with csDMARDs) was equivalent in elderly and younger patients
Lane *et al.* [53]	Cohort of 20 814 veterans (mean age 63 years) with RA, including 3796 anti-TNF-treated patients. Rate of hospitalization for SI was compared with csDMARD users (mean follow-up 2.7 years)	No assessment	In multivariate analysis, unlike csDMARD use, anti-TNF use was associated with hospitalization for infection (HR = 1.24; 95% CI: 1.02, 1.50)
Curtis *et al.* 2012 [54]	Prospective cohort of 11 657 RA patients (mean age 61.9 years) initiating anti-TNF therapy. The observed 1-year rates of infection were compared with a predicted infection risk score estimated in the absence of anti-TNF exposure	No assessment	The rate of SI for anti-TNF agents was increased incrementally by a fixed absolute difference irrespective of age (above *vs* below 65 years)
Herrinton *et al.* [64]	Cohort of 46 424 patients with selected autoimmune diseases. Mortality was compared between new anti-TNF users and similar new csDMARDs users	No assessment	Anti-TNF therapy was associated with a reduction in mortality among RA patients with ⩾2 co-morbid conditions (aHR = 0.87; 95% CI: 0.77, 0.99), or age ⩾75 years
Toh *et al.* [57]	Retrospective study of 3485 RA patients (mean age 57.9 years) who initiated INF or ETA. Rate of SI or opportunistic infections during the first year was compared between infliximab initiators and etanercept initiators	No assessment	Rate of SI per 100 person-years was 5.4 (95% CI: 3.8, 7.5) in patients <65 years and 16.0 (95% CI: 10.4, 23.4) in patients ⩾65 years during the first 3 months following treatment initiation. The increased risk of SI associated with infliximab compared with etanercept in young subjects disappeared in patients >65 years of age

(continued)

Table 1 Continued

References	Design	Efficacy	Tolerance
Dreyer *et al.* [65]	Register of RA patients (mean age 58 years). The incidence of cancer in patients treated with ($n = 3347$) or without TNF inhibitors ($n = 3812$) was evaluated over a mean follow-up of 2.5 years	No assessment	TNF antagonist-treated patients did not exhibit an increased risk of overall cancer (HR = 1.02; 95% CI: 0.80, 1.30) compared with non-treated patients, even >65 years of age (HR = 1.10; 95% CI: 0.80, 1.50)
Payet *et al.* [34]	Prospective register of 1709 RA patients (including 191 aged ⩾75 years and 417 aged 65–74 years) aiming to compare the efficacy and safety of RTX as a function of patient age	Patients aged 65–75 years were more likely to be good responders than non-responders at 1 year of follow-up than patients age ⩾75 years (OR = 3.81, 95% CI: 1.14, 12.79). After the sixth month, the decrease in DAS 28 score was less marked in the population aged >75 years than in the group aged <50 years	At 24 months, no significant difference was shown among the groups for SAE or RTX discontinuation rates. The reasons for discontinuation (inefficacy, AE) were the same in all four groups. Infections were more common in the elderly
Wu *et al.* [66]	Nationwide cohort of RA patients in Taiwan including 4426 treated with biologics and 17 704 matched patients taking csDMARDs only, with a median follow-up of 3 years aiming to compare the SIRs of cancer	No assessment	Incidence of cancer was reduced in biologic users in almost all subsets of study subjects, especially among those aged >60 (HR = 0.56; 95% CI: 0.40, 0.79), with disease duration >10 years (HR = 0.43; 95% CI: 0.24, 0.77). However, there was an increased risk for haematological cancers in the biologics cohort (SIR = 4.64; 95% CI: 2.65, 7.53)
Pers *et al.* [38]	Retrospective study of 222 RA patients (including 61 aged ⩾65 years) aiming to assess the safety and efficacy of TCZ in daily practice considering two age groups: <65 years (<65) and ⩾65 years	After 6 months, the ERA less often reached remission (27.8 *vs* 45.6%; $P = 0.02$) or good EULAR response (40.7 *vs* 61.0%; $P < 0.01$) compared with YRA	Drug maintenance for TCZ and adverse event discontinuation rates were similar between the two age groups
Sekiguchi *et al.* [14]	Prospective cohort of 277 RA patients with high or moderate disease activity receiving ABA as an initial boDMARD to differentiate predictive factors of sustained clinical remission between YRA and ERA	Clinical remission was similarly achieved between ERA (at 24 and 48 weeks in 35.1 and 36.5%) and YRA (34.9 and 43.4% at 24 and 48 weeks)	No significant differences in the treatment withdrawal rates owing to adverse events depending on age
Lahaye *et al.* [35]	Prospective registry of 1017 RA patients (including 103 ⩾75 years and 215 between 65 and 74 years) to study the effect of age on the risk–benefit balance of ABA with a 2-year follow-up	The EULAR response (good or moderate) and remission rate were not significantly different according to age. At 6 months, the very elderly had a significantly lower likelihood of a good response than the very young (OR = 0.15, 95% CI: 0.03, 0.68). The decrease in DAS 28-ESR over the 24-month follow-up period did not differ by age	Increasing age was associated with a higher rate of discontinuation for AE, especially SIs (per 100 patient-years: 1.73 in very young, 4.65 in intermediates, 5.90 in elderly, 10.38 in very elderly; $P < 0.001$)

(continued)

Table 1 Continued

References	Design	Efficacy	Tolerance
Kawashima *et al.* [56]	Retrospective study of 183 RA patients over the age of 65 years treated with bo or csDMARDs over a 3-year observation period to determine the risk factors of SI	No assessment	The incidence rate of SI per 100 person-years was not significantly different between biologics-treated (8.0; 95% CI: 4.7, 13.5) and non-biologic DMARD-treated patients (6.3; 95% CI: 4.1, 9.5, $P = 0.78$). Prednisolone was associated with SI only in biologics-treated patients at 1–4 mg/day, and in both groups at >5 mg/day
Curtis *et al.* [39]	Pooled data from five phase 3 trials and separately from two open-label long-term extension studies concerning RA patients who received tofacitinib or placebo (phase 3 only), with/without csDMARDs, aiming to compare efficacy and safety outcomes between older (aged ⩾65 years, 1136/7213) and younger patients	In phase 3 trials, at 3 months, probability ratios for ACR responses and HAQ-DI improvement from baseline ⩾0.22 favoured tofacitinib (5 and 10 mg BID). ACR responses were similar in ERA and YRA, but HAQ-DI ⩾0.22 appeared to be somewhat lower for older tofacitinib-treated patients than for YRA	Compared with YRA, ERA treated with 5 mg BID were more exposed to SAEs (IR = 17.6; 95% CI: 14.1, 21.9 *vs* 8.4; 95% CI: 7.4, 9.6), SI (IR = 3.9; 95% CI: 2.5, 6.0 *vs* 2.4; 95% CI: 1.9, 3.0) and discontinuation due to AEs [IR = 9.2 (95% CI: 7.0, 12.3) *vs* 6.0 (95% CI: 5.2, 7.0)]. This risk signal was similar with the 10 mg BID dosage

ABA: abatacept; ADA: adalimumab; aHR: adjusted hazard ratio; BID: bis in die; boDMARD: biologic originator DMARD; csDMARD: conventional synthetic DMARD; EORA: elderly-onset RA; ERA: elderly RA patients; ETA: etanercept; IR: incidence rate; HR: hazard ratio; INF: infliximab; KIN: kineret; NMSC: non-melanoma skin cancer; OR: odds ratio; RR: risk ratio; RTX: rituximab; SAE: serious adverse event; SI: severe infection; SIR: standardized incidence ratio; TCZ: tocilizumab; YORA: younger-onset RA; YRA: Young RA patients.

MTX has been associated with serious AEs, such as major infections, hepatic failure, bone marrow depression and inflammatory pneumonitis. In a Canadian population-based study, increasing age was associated with an increased tendency towards MTX discontinuation in newly diagnosed RA patients [43]. As kidney failure and hypoalbuminaemia both increase the risk of severe MTX toxicity, a dose adjustment is often necessary in the elderly [18, 44, 45]. In a retrospective series of 90 LEF-treated RA patients (monotherapy or combination therapy) with 2 years of follow-up, the AEs and survival rates of LEF were equivalent between patients aged ⩽65 years and those aged >65 years [20]. However, hypertension and unintentional weight loss related to LEF are of particular concern in the elderly [46].

Regarding TNFi, several studies have pointed out high infection risk in the elderly (Table 1) particularly in cases of high comorbidity, elevated disease severity markers and previous infection [42]. In retrospective cohorts of RA patients treated with biologic originator DMARDs (boDMARDs), though drug discontinuation appeared similar between age groups; discontinuation was related mainly to AEs (specifically infections) in the elderly, whereas drug ineffectiveness was the main reason for treatment discontinuation in younger patients [47–50]. In a registry of RA patients treated with conventional DMARDs or TNFi, multivariate analysis revealed that TNFi use (risk ratio (RR) = 2.37; 95% CI: 1.11, 5.05; $P = 0.026$) and age (by decade RR = 1.82; 95% CI: 1.32, 2.52; $P = 0.00031$) were significant independent risk factors for serious infections [51]. A moderately increased absolute risk of serious infection has been reported after the introduction of TNFi, with no difference between age categories [23, 52–54]. However, after multivariate adjustment for age, sex and comorbidities, most of the studies did not find an increased risk of serious infection associated with the initiation of TNFi therapy compared with non-biologic comparators [55], even upon long-term follow-up [29, 30, 56] and irrespective of the inhibitor [57].

Compared with TNFi therapy-naïve subjects, patients on TNFi therapy are more susceptible to tuberculosis reactivation, usually affecting extrapulmonary sites (pericardium, gastrointestinal, bone or lymph nodes) [67]. Age >60 years for RA, history of tuberculosis and daily GC use ⩾5 mg were significant risk factors for this complication [68, 69].

In addition, ageing RA patients are at particular risk of herpes zoster (HZ) infection. The incidence of HZ infection appears to be similar after initiating csDMARD or TNFi therapy, regardless of the inhibitor that is used [70]. Age and GC use are additional risk factors [56, 57]. As a representative of the emerging class of Janus kinase inhibitors, tofacitinib seems to increase the risk of opportunistic infections such as tuberculosis and HZ infection [71]. Thus, the ACR recommends the HZ vaccine for all RA patients aged $\geqslant$50 years, before the introduction of boDMARDs due to it being a live vaccine [72].

Though data on other biologics are scarce, they suggest an increased risk of infection (Table 1). Concerning abatacept, two cohorts found no significant differences in treatment withdrawal rates due to AEs depending on age [14, 37]. This outcome differed from the French registry, in which increasing age was associated with a higher AE-induced treatment discontinuation rate, especially in regards to severe infections [35]. In a Japanese registry, the elderly abatacept-treated group ($>$69.5 years) demonstrated higher incidence rate of discontinuation due to AEs in patients without concomitant use of MTX [36]. Concerning rituximab, even if one prospective study showed no effect of age on ADRs and serious ADRs [33], other studies with long-term follow-up revealed that age $>$65 years is associated with a higher incidence of discontinuation rates due to serious ADR [73] or infections compared with age $<$65 years [34]. In a retrospective study pertaining to tocilizumab use in RA patients, drug maintenance was similar between elderly and younger RA patients. No differences were found according to age class [38]. In a pooled analysis pertaining to three randomized controlled trials and two open label extensions in tofacitinib-treated patients with moderate to severe RA, serious infections and AE-induced discontinuations are more common after 65 years of age [39]. Similar results were observed with baracitinib [74]. In addition to differences in the mode of action among DMARDs, the differing infectious risks may reflect an incomplete adjustment for infection risk factors in elderly RA patients (e.g. diabetes, malnutrition).

Among pharmacological risk factors for infection, the use of GCs plays a predominant role. Oral GC at doses $\geqslant$5 mg prednisone-equivalent are associated with a dose-dependent increase in serious infection risk, which is still present up to 2 years after discontinuing treatment [55, 56, 67]. Moreover, low GC doses (1–4 mg/day) have been shown to be associated with serious infections in biologics-treated patients, but not in non-biologic DMARD-treated patients [56]. Specific studies on the benefit/risk balance of GCs in the elderly will be particularly useful.

Elderly patients are at particular risk for cancer, and RA is associated with an overall increased incidence of cancer, especially Hodgkin's and non-Hodgkin's lymphoma [75], and non-melanoma skin cancers [76]. Moreover, elderly RA patients who develop cancer have a higher mortality rate than subjects without RA after controlling for other comorbidities [77]. As biotherapies are suspected to play a role in carcinogenesis and tumour progression, cancer risk during boDMARDs treatment have been observed in numerous studies, with discordant results, particularly due to the disparate methodologies used (follow-up period, comparator, cancer type, etc.) [78, 79]. Notably, increased crude rates of cancer have been reported in EORA *vs* YORA patients undergoing TNFi treatment [23] or other biotherapies [35]. However, most of the studies did not reveal an increased overall cancer risk using TNFi [60, 65, 79, 80] or other biologics [58, 66] compared with csDMARDs in elderly patients. Although specific risks of haematological cancers [66] and non-melanoma skin cancer [63, 81] have been reported in TNFi-treated patients compared with biologic-naïve patients, these studies were not specific to older subjects. Current knowledge advocates the monitoring of increased cancer risk in elderly patients, starting at diagnosis and continued *a fortiori* prior to and after biotherapy initiation.

RA is associated with an increased risk of early cardiovascular diseases [82, 83]. Due to inflammatory mediators playing a role in the pathogenesis of cardiovascular diseases, TNFi were expected to exert a protective effect [82]. Though such a benefit was observed in a younger patient population [84], elderly patients receiving TNFi exhibited a higher hospitalization rate for heart failure (HF) than patients on MTX [85], but without increased mortality [64]. In a retrospective US cohort of RA patients, TNFi were associated with higher acute myocardial infarction risk compared with abatacept [86]. However, in another American database of RA patients starting TNFi or boDMARD treatment after MTX use, there was no elevation in HF risk among users of inhibitors, irrespective of prior HF. Oral GCs were associated with a dose-dependent increase in HF risk [78].

Due to chronic inflammation, functional limitation and associated treatments, especially GCs, RA is associated with an increased risk of both fracture and sarcopenia. Besides traditional risk factors, such as low BMI or oral GC use, RA duration $>$10 years is associated with an elevated risk of hip fracture [87]. Due to the specific risk linked to prolonged GC use [88], the ACR has established lifestyle and pharmacological recommendations for preventing and treating GC-induced osteoporosis [89].

Place of the elderly in the recommendations

The 2015 Guidelines of the ACR and 2016 EULAR recommendations do not include recommendations regarding the elderly [16, 72]. However, comorbidities and safety issues should be taken into account when therapeutic adjustments are required. Specific EULAR recommendations reaffirm the relevance of managing the higher cardiovascular disease risk, not only in patients with RA, but also in those with SA or PsA. The necessity of using NSAIDs and GCs sparingly has also been stressed [90], but recommendations concerning GC use in elderly RA patients are lacking [22].

SpA and PsA

Specificities of initial presentation in the elderly

Only 5% of SP patients are >50 years of age. These late-onset SP cases may present distinctive characteristics: constitutional signs, cervical involvement, predominant peripheral arthropathy of the upper and lower limbs and more frequently mixed forms, namely axial and peripheral joint disease [91–93].

Data on elderly patients mostly concern PsA, which occurs in 6–42% of psoriasis. Although arthritis may precede the onset of psoriasis by many years, the common scenario is that the onset of psoriasis is 10 years before PsA [94]. PsA has a more severe onset and more destructive outcome in the elderly than in younger subjects [95]. Elderly-onset PsA patients are characterized by higher rates of fatigue, pain scores, comorbid diseases and acute phase reactants and less dactylitis and nail involvement than young-onset PsA [96].

PsA is associated with increased mortality, most commonly with cardiovascular causes [97]. PsA, as well as ageing and tobacco use, is an independent risk factor of subclinical atherosclerosis (explored by intima–media thickness) [98]. Patients with AS also exhibit a higher risk of myocardial infarction and stroke [99], but no specific study has addressed elderly patients. Yet, screening for cardiovascular risk factors by physicians proves insufficient [100], resulting in under-treatment [101].

PsA patients exhibit a higher risk of opportunistic infections and haematological cancer [102] than matched controls, partly linked to immunosenescence [103]. In the CORRONA registry, the adjusted incidences of overall malignancy and cancer subtypes, including non-melanoma skin cancer and lymphoma, were similar in PsA and RA patients, increasing with age, without a significant difference between csDMARD and boDMARD cases [104]. PsA also potentiates the risk of osteopenia, osteoporosis and pathological fractures in the elderly [105].

Age and treatment effectiveness

Therapeutic efficacy and safety data in elderly PsA patients are limited (Table 2) [106, 107]. The efficacy of csDMARDs could be lower than that of boDMARDs in the elderly [108]. Biologics and conventional systemic therapies appear to be as effective in the elderly as in adult patients with moderate-to-severe Pso [109–111]. In a conflicting study involving 146 consecutive PsA patients initially undergoing TNFi treatment, age inversely correlated with minimal disease activity at 3 months [112]. Most authors reported a favourable risk/benefit ratio for long-term use of TNFi therapy in elderly Pso patients [110, 113, 114].

Age and adverse drug reactions

Data concerning the effect of age on the occurrence of AEs, including infection rates for both biologics and conventional systemic treatments, appear to be inconsistent [103, 109, 115], whereas conventional systemic treatments are more frequently discontinued in the elderly due to AEs compared with biologics. Similar to RA, TNFi exhibit an increased risk of reactivating latent tuberculosis in Pso patients, thereby requiring adequate screening and prevention strategies [116]. In AS, the risk of tuberculosis is elevated during TNFi therapy, and BMI $<22\,kg/m^2$ is a significant risk factor in this complication [68]. In a large-scale US cohort, the use of TNFi was not associated with increased mortality in patients with Pso, PsA or AS compared with non-biologic therapies, regardless of the drug used, even after 75 years [64]. In the DANBIO registry, patients on TNFi therapy for PsA or AS did not exhibit an increased incidence of cancer compared with TNFi-naïve patients, regardless of age [65]. Recently, ustekinumab has exhibited adequate efficacy and safety [117, 118]. In the Psoriasis Longitudinal Assessment Registry (38% of PsA), long-term (⩾12 months) treatment with a TNFi, but not MTX and ustekinumab, seemed to increase the risk of malignancy [119]. However, larger sample sizes and longer observation duration will be required to confirm the safer profile of ustekinumab compared with other TNFi in elderly Pso patients.

Despite the limited data on biologic drugs (Table 2), biologics seem to be an effective and safe alternative to conventional systemic agents in the elderly PsA population.

Place of the elderly in the recommendations

Three recommendation sets for PsA management have been published in the past 2 years [120–122]. Though no reference has been made to age, the impact of disease on pain, function, HR-QoL and other potentially related conditions (e.g. cardiovascular disease, malignancy, osteoporosis), as well as drug-related risks, should be considered in order to determine individualized targets. All guidelines recommend multidisciplinary and multispecialty assessment and management. In the UK guidelines of the British Association of Dermatologists concerning Pso, age, history and comorbid conditions should be considered when choosing the optimal biologic therapy, with no more details given [123].

Ways to improve care of the elderly

Limit inappropriate prescribing

The lack of specific studies triggers fears of side effects or insufficient disease control by both the patient and prescriber, leading to innovative therapeutic strategies being least used in the elderly [75]. This results in an underuse of DMARDs, especially the biologics, at the cost of an excessive use of old treatments with uncertain risk/benefit balance (NSAIDs, GCs) [11, 13, 59, 124, 125]. Though effective and inexpensive, GCs are potentially responsible for hypertension, insulin resistance, weight gain, osteoporosis, fractures, infections, gastric ulcers, adrenal suppression and mortality [88], and NSAIDs can promote drug interactions, renal failure, cardiovascular events and gastrointestinal bleeding [126]. However, specific data in the elderly population are rare, and ongoing studies such

Table 2 The efficacy and safety of boDMARDs in elderly patients with SpA and PsA

References	Design	Efficacy	Tolerance
Militello *et al.* [111]	*Post hoc* analysis of two large phase 3 randomized placebo trials of etanercept in psoriasis including 77 elderly (⩾65 years old) and 1158 younger patients	The elderly and young patients did not differ with regard to the number of patients reaching PASI 50 or PASI 75 at week 12 and at any of the three dosing regimens. Both the elderly and young had similar improvement in quality of life (DLQI) with therapy	Although dropout rates were similar at week 12, there was a significant increase in SAE in the elderly group across all cohorts. These events were not associated with treatment
Menter *et al.* [110]	A phase 3 randomized controlled evaluation of adalimumab with every other week dosing in 1212 patients with moderate to severe psoriasis. *Post hoc* subgroup analyses were conducted to determine factors associated with adalimumab efficacy	PASI 75 score responses at week 16 were uniformly strong across subgroups, including age, 10-kg weight intervals, BMI and PsA history groups Older patients (⩾65 years), tended to respond as well as younger patients	Adalimumab had an acceptable safety profile and was well tolerated at week 16 regardless of the presence of comorbidities
Iervolino *et al.* [112]	A prospective cohort of 146 consecutive patients with PsA eligible for TNF inhibitor therapy was used to identify predictors of early minimal disease activity at 3 months	Age (OR = 0.896, $P = 0.003$) and BASFI (OR = 0.479, $P = 0.007$) inversely predicted, whereas CRP (OR = 1.78, $P = 0.018$) directly predicted, achievement of minimal disease activity at 3 months	No assessment
Esposito *et al.* [114]	Retrospective analysis of 89 patients with plaque-type psoriasis and PsA ($n = 62$) aged ⩾65 years undergoing subcutaneous administration of ETA or ADA aiming to evaluate the long-term efficacy and safety profile	In patients with PsA treated with ETA, the mean DAS44-ESR score decreased from 5.80 to 2.29 after 12 weeks and to 0.89 at 3 years, and the mean Pain-VAS score from 75.10 to 19.47 at week 12 and to 3.15 at 3 years. In patients with PsA treated with ADA, the mean DAS44-ESR score decreased from 3.43 to 2.45 after 12 weeks and to 1.44 at 3 years, and the mean Pain-VAS score from 71.30 to 35.91 at week 12 and to 18.26 at 3 years	The survival rate after 3 years of treatment was 75.40 and 60.71% for ETA- and ADA-treated patients, respectively. Safety profiles of the two treatments were similar. Loss of efficacy was the major cause of treatment interruption. Injection site reactions, weight gain of ⩾5 kg and upper respiratory tract infections were the most common adverse events
Hayashi *et al.* [117]	Retrospective study of 24 patients with moderate to severe plaque psoriasis aged >65 years (mean, 73.1 years) aiming to evaluate the efficacy and safety profile of UST (at weeks 0 and 4, and then every 12 weeks) over a 1-year period	PASI 75 responses were 56.5% at week 16, 59.1% at week 28 and 60.0% at week 52 The mean DLQI score decreased from 7.8 (6.0) to 2.5 (3.4) at week 16, and 1.2 (1.7) at 1 year	One patient developed a mild urinary tract infection, but no serious infection was reported during the 1-year treatment. Two patients developed arthritis and improved after switching to ADA
Piaserico *et al.* [108]	Prospective registry with 187 elderly patients with psoriasis (PsA 26%) receiving a new treatment with csDMARDs or boDMARDs	At week 12 of therapy, PASI 75 was lower with traditional drugs (49, 27, 46 and 31% for MTX, acitretin, ciclosporin and PUVA, respectively) than with boDMARDs (64, 65, 93, 57 and 100% for etanercept, adalimumab, infliximab, efalizumab and ustekinumab, respectively)	The rate of adverse events was 0.12, 0.32, 1.4 and 0.5 per patient-year in the MTX, acitretin, ciclosporin and PUVA groups, respectively. Etanercept was associated with a lower rate of adverse events compared with other boDMARDs (0.11 *vs* 0.35, 0.19, 0.3 and 0.26 for etanercept, adalimumab, infliximab, efalizumab and ustekinumab, respectively)
Medina *et al.* [115]	Registry of psoriatic patients treated with systemic therapy including 175 elderly (⩾65 years old) and 1618 younger patients. Adverse event rates were compared taking into account exposure to classic or biologic drugs	No assessment	SAEs were more common in elderly (drug group-adjusted HR = 3.2; 95% CI: 2.0, 5.1). Age-adjusted HR of all adverse events was lower for patients exposed to boDMARDs compared with csDMARDs (HR = 0.7; 95% CI: 0.6, 0.7)

(continued)

Table 2 Continued

References	Design	Efficacy	Tolerance
Garber *et al.* [109]	Retrospective cohort of psoriatic patients including 48 elderly (⩾65 years old) and 146 adult (18–64 years old) patients	There was no significant difference in S-MAPA improvement at 12 weeks between the two cohorts when treated with biologics or conventional systemics. Within the elderly cohort, there was no significant difference in the efficacy of biologics *vs* conventional systemics at any time point	For both boDMARDs and csDMARDs, there was no significant intergroup difference in the rate of adverse events or infection. Elderly patients had a higher rate of adverse events with csDMARDs than with boDMARDs ($P = 0.033$)
Megna *et al.* [118]	Retrospective study of 22 patients with psoriasis aged ⩾65 years treated with UST at weeks 0 and 4, and then every 12 weeks for at least 2 years	PASI 75 was reached in 63.6% ($n = 14$), 86.4% ($n = 19$) and 90.9% ($n = 20$) of patients after 28, 52 and 100 weeks, respectively	Over 2 years, no cases of serious infections were reported; only two mild adverse events were registered (one liver enzyme elevation and one hyperglycaemia)

ADA: adalimumab; BASFI: Bath Ankylosing Spondylitis Functionnal Index; DLQI: Dermatology Life Quality Index; boDMARD: biologic originator DMARD; csDMARD: conventional synthetic DMARD; ETA: etanercept; HR: hazard ratio; OR: odds ratio; PASI: Psoriasis Area and Severity Index; PUVA: Psoralen and UltraViolet A; SAE: serious adverse event; SI: severe infection; S-MAPA: Simple-Measure for Assessing Psoriasis Activity; UST: ustekinumab.

as GLORIA (risk benefit of low dose steroids in elderly RA patients, [127]) will be needed to clarify the place of these molecules in elderly management.

Even though the prescription of boDMARDs has progressed in RA over the last decade, the use of these drugs remains less common in elderly patients [13, 59, 124, 125, 128–132], despite comparable or even higher disease severity and activity [24]. Other common characteristics found in the elderly are associated with a lower likelihood of boDMARD initiation, including less education [133], low income and living alone [134]. Elderly psoriasis patients tend to be treated with biologics less frequently than younger patients [103, 109, 115]. Even with an equivalent or higher severity of PsA, the elderly tend to be treated less with TNFi than young patients [96].

As in other chronic diseases, polypharmacy is particularly frequent in IRD and can promote drug–drug interactions, ADRs and non-adherence [135]. Moreover, in the elderly, polypharmacy is also associated with cognitive impairment, falls and malnutrition [136]. Various strategies have been developed to minimize inappropriate prescribing in multimorbid older people, such as prescriber education in geriatric pharmacotherapy, routine application of STOPP/START (screening tool for older people's prescriptions/screening tool to alert to right treatment) criteria, electronic prescribing and close liaison between clinical pharmacists and physicians [137].

Look for comorbidities to refine the prognosis

The elderly population is characterized by great heterogeneity. Thus, comorbidities and functional limitations are not only determinants of poor HR-QoL, dependency and excess mortality in the elderly [138–140], but are relevant prognostic factors in the treatment response. Yun *et al.* reported that use of antidepressants, narcotics or GCs at a dose >7.5 mg at baseline in Medicare RA patients was associated with lower biologic effectiveness (TNFi and abatacept) [141]. The biologic effectiveness was greater among non-disabled persons compared with disabled patients (RR = 18; 95% CI: 1.08, 1.28). These results are consistent with data from other studies showing that disability, low functional status and concomitant GC use are inversely associated with the clinical response to treatment with TNFi [25, 28]. Other studies have revealed an inverse relationship between the number of comorbid conditions and the probability of attaining remission [124, 129].

In addition to lower efficacy, comorbidities and functional impairment are associated with more side effects. Renal insufficiency has been known for a long time to be a major determinant of MTX toxicity [18] due to impaired MTX elimination [142]. In a registry of 309 MTX-treated patients (first DMARD), the HAQ score (odds ratio = 1.84; 95% CI: 1.12, 3.01) was significantly associated with AEs at 1 year [143]. In retrospective cohorts of boDMARD-treated patients, the presence of comorbidities such as chronic pulmonary disease [48, 51], renal diseases [144] or diabetes mellitus [145] was associated with certain AEs, particularly infectious disease, whereas low functional status and concomitant GC use (>5 mg prednisolone per day) were associated with a higher incidence of AEs [144, 145]. In the German biologics registry RABBIT, comorbidities and persistent, highly active disease (mean DAS 28 score >5.1) were significantly associated with increased mortality, even in patients >65 years of age [146].

A comprehensive assessment serving a global strategy

A comprehensive geriatric assessment is a systematic, multidimensional and multidisciplinary approach designed to collect data regarding the medical, nutritional, thymic, social and functional status of elderly patients. This assessment has proven very useful for building an integrated

and personalized therapeutic project including pharmacological and non-pharmacological interventions, while preserving HR-QoL and autonomy and limiting mortality [147]. In particular, screening and preventing depression, denutrition and mobility limitations are efficacious ways of improving the HR-QoL and survival of the elderly.

A meta-analysis of 72 studies including 13 189 RA patients revealed that depression is highly prevalent (between 15 and 35% according to the type of criteria used), even if older patients seem to be at lower risk than younger subjects [148]. In a German longitudinal database, depression was present in 22% of the 1072 elderly RA patients (mean age 72 years), and dementia, cancer, osteoporosis, hypertension and diabetes were associated with a higher risk of developing depression [149]. Moreover, depression is associated with increased global mortality in RA [150], suicide death in RA and PsA [151], and reduced likelihood of joint remission in RA and PsA [152, 153]. However, anti-depressants are frequently associated with side effects and have inconstant benefits in pain management or functional status [154]. More specific studies would be needed to evaluate the interest of pharmacological and non-pharmacological treatment for depressed elderly [155].

Rheumatoid cachexia is characterized by an involuntary reduction in lean body mass (LBM) associated with normal or even increased fat mass [156], and is observed in 26–71% of RA patients [157]. Low muscle function is often related to this low LBM, defining sarcopenia [158]. As bone and muscle are critically linked, low LBM and higher fat mass are associated with osteopenia, even after adjusting for age, race, gender and height [159, 160]. Major fractures and sarcopenia are essential prognostic issues in the elderly for both HR-QoL and mortality [161–163]. In RA, the negative effect of low lean mass on walking speed is potentialized by ageing, depression, pain, cumulative GC exposure and non-treatment with DMARDs [164]. Adequate control of disease activity in combination with appropriate physical exercise and increased calcium/vitamin D and protein intake are efficient strategies for controlling rheumatoid cachexia, cardiovascular risk and risk of fracture, and preserving autonomy [156, 165, 166]. Thus, all types of physical activities, including walking or aerobic and strengthening exercises, have exhibited modest benefit in cardiovascular risk, disease-related outcomes, inflammation and HR-QoL in IRD, but without significant side effects [167, 168].

Concerning nutritional intervention, the effects of antioxidant-rich and omega-3 fatty acid-rich diets (e.g. Mediterranean diets) are inconsistent [169]. A high dose omega-3 regimen (3–5 g/day) has been shown to improve disease-related activity markers in RA [170]. Restrictive diets and fasting, although potentially effective on disease activity in healthy middle-aged patients, could be particularly deleterious in the aged subject and must be avoided. Thus, no study has been conducted specifically with elderly subjects.

Towards new study designs to support specific recommendations

Although current studies are more interested in the elderly population, they continue to evaluate the benefits of interventions using tools best adapted to younger patients. Regarding the elderly, the actual value given to clinical/biological/radiological criteria for activity seems rather disproportionate. The clinical relevance of therapeutic strategies should be assessed by their impact on HR-QoL, autonomy and mortality related to cardiovascular diseases or cancers. This will require broader criteria and longer-term assessments. These new evaluation criteria should then be considered in management strategies, which currently almost exclusively consider the IRD activity criteria [16].

Recent therapeutic developments have occurred rapidly, particularly when considering non-TNFi biologics. Their precise place among the therapeutic strategies needs to be re-evaluated: as second-line after relapse or as first-line in patients at risk of complications with conventional treatments. This issue appears to be particularly relevant for frail comorbid subjects. Therefore, further studies will be required to validate the most effective therapeutic strategies to best adapt the existing recommendations and guidelines.

Conclusion

In conclusion, IRD management in the elderly is a permanent challenge due to wide heterogeneity in terms of autonomy and comorbidity, several specificities in terms of the clinical presentation and treatment response, and a scarcity of specific literature pertaining to this patient population. Based on an increasing amount of data, biologic treatments appear to be useful tools for controlling disease activity and reducing iatrogenicity in severe IRD, even in the elderly population, limiting the use of more dangerous systemic drugs, such as GCs and NSAIDs. However, elderly patients often remain deprived of effective therapies, primarily due to age. A multidimensional health assessment should be performed in order to build up an integrated therapeutic strategy.

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