Joint Bone Spine 82 (2015) 154–160

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Review

Overview of biologic treatments in the elderly

Clément Lahaye [a], Zuzana Tatar [b], Jean-Jacques Dubost [b], Martin Soubrier [b,*]

[a] CHU (University Hospital Center) Clermont-Ferrand, Department of Internal Medicine, Hôpital Estaing, Clermont-Ferrand, France
[b] CHU Clermont-Ferrand, Department of Rheumatology, Hôpital Gabriel Montpied, Clermont-Ferrand, France

ARTICLE INFO

Article history:
Accepted 22 October 2014
Available online 29 December 2014

Keywords:
Elderly
Biotherapies
Inflammatory rheumatism
Efficacy
Safety
Management

ABSTRACT

As life expectancies rise, the number of elderly people with inflammatory rheumatic diseases will continue to grow. Treatment of this frail population, whose clinical features differ from those of younger subjects, poses new challenges to healthcare systems. However, this issue is rarely addressed in the current literature. Thanks to their targeted mechanism of action, biologics represent one of the major therapeutic advances of the last 15 years, but their use in the elderly has been slow in developing. Published data, derived mainly from cohorts, focus on the use of TNF inhibitors in rheumatoid arthritis and show that these treatments are effective and generally well tolerated. Nevertheless, the risk of infection and cancer, particularly skin and lymphoid malignancies, must not be neglected. The use of these biologics as second-line treatment improves patient outcomes and comfort, while reducing consumption of the widely used and more deleterious drugs such as glucocorticoids and non-steroidal anti-inflammatory drugs. Additional studies on biologics, focusing on the longer term and in indications apart from anti-TNF therapies in rheumatoid arthritis should help overcome some of the reluctance and promote the rational use of these drugs in the elderly.

1. Introduction

The aging of the population is a defining characteristic of the western world. In France, one-third of the population will be over the age of 60 by the year 2050, as compared to only 20% in 2005 [1]. This will lead to profound economic and epidemiological upheaval and create new challenges for our healthcare systems. The proportion of chronic inflammatory rheumatic diseases diagnosed in people aged over 60 is on the rise; as an example, 30% of rheumatoid arthritis (RA) cases occur in this age category. At the same time, medical research now offers clinicians a new class of maintenance therapies known as biologics, composed of specific antibodies with immunomodulating properties. Introduced in the late 1990s, biologics represent a major development in the management of rheumatoid arthritis. In addition to TNF (Tumoral Necrosis Factor) antagonists (infliximab, etanercept, adalimumab, certolizumab pegol, golimumab), targeted therapies now exist for other key inflammatory mediators, including both cytokines (IL-1, i.e., Interleukine 1, for anakinra, IL-6 for tocilizumab) and cell-derived mediators (CTLA-4, i.e., Cytotoxic T-Lymphocyte-Associated Protein 4, for abatacept, anti-CD20, i.e., Cluster of Differentiation, for rituximab). The efficacy of these agents has since been demonstrated in many other chronic inflammatory diseases, such as ankylosing spondylitis (AS), inflammatory bowel disease (IBD), psoriasis (Pso), psoriatic arthritis (PsoA), juvenile idiopathic arthritis, multiple sclerosis, systemic lupus erythematosus, gout or cryopyrin associated periodic syndrome, but their novel mode of action has also raised concerns about safety and side effects.

We reviewed the latest data on the benefits and risks of these biologic therapies in rheumatologic diseases of the elderly. As most of the studies concern anti-TNF therapies in RA, we will focus on this population.

2. An understudied and atypical population

Age is a risk factor for many comorbidities (diabetes, obesity, renal failure etc.) and also modifies drug pharmacokinetic parameters (absorption, distribution, metabolism and excretion), which vary widely from one individual to another. These age-related characteristics make clinical studies difficult to interpret. Prospective control and cohort studies strive to have a homogeneous study population and therefore often exclude elderly subjects and thus select volunteers with fewer comorbidities compared to a global population of patients at the same age [2]. This selection compromises the extrapolation of results to the "real life" elderly. Registries, even

* Corresponding author. CHU Clermont-Ferrand, Department of Rheumatology, Hôpital Gabriel Montpied, 63003 Clermont-Ferrand, France.
E-mail address: msoubrier@chu-clermontferrand.fr (M. Soubrier).

http://dx.doi.org/10.1016/j.jbspin.2014.10.012
1297-319X/

though they are not without bias, follow patients in a real-life setting and are a crucial source of information for guiding clinical practice. Otherwise, clinical studies use the chronological age of 60 or 65 years as a definition of "elderly" and over 75 years as "very elderly". Such a choice may seem somewhat arbitrary as the definition of an elderly person varies across centuries and continents. Biological age, by integrating the aging of organs, comorbidities and functional limitations, could be much more relevant to define a geriatric patient. However, in the absence of consensus on the calculation of biological age, the chronological cutoff remains the most widely used, in agreement with the World Health Organization [3].

Patients with RA treated with anti-TNFs constitute an ideal group for assessing the benefits and risks of biologic treatment in the elderly. First, anti-TNFs are among the oldest biologics and are still by far the most widely used and have the longest follow-up in RA. Second, patients with RA tend to be older and have more comorbidities than those with other inflammatory diseases (IBD, AS). Data on the other biologics and other inflammatory diseases are less robust.

Although rarely studied, inflammatory rheumatic diseases have a different presentation and a distinct course in the elderly, making it risky to establish guidelines based on data extrapolated from younger age groups. This situation is evident in the case of elderly-onset RA (EORA), i.e., onset after 60 years of age. Clinically, female bias is less marked, onset is more abrupt, morning stiffness is prolonged and constitutional symptoms are more severe than in younger-onset disease [4]. It also more selectively affects the proximal joints such as the shoulders, complicating the differential diagnosis with polymyalgia rheumatica or microcrystalline arthritis [5]. Although elderly RA patients had a higher DAS28 (Disease Activity Score) and Ratingen score at diagnosis, they did not differ from young patients in terms of the rate of radiological progression after 5 years of treatment [6]. In spondyloarthropathies, patients over 50 account for only 5% of all patients, but their distinctive features have long been recognized [7]; the clinical presentation includes constitutional signs, cervical involvement and more frequent peripheral arthropathy [8]. PsoA has a more severe onset and a more destructive outcome in the elderly compared with young subjects [9].

3. The era of tight control?

The goals of RA treatment are to control pain, maintain quality of life, prevent structural damage and preserve function over the long-term. Conventional drug therapy is based on maintenance treatment with DMARDs (methotrexate primarily, sulfasalazine, leflunomide and hydroxychloroquine) in combination with non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and analgesics. Although glucocorticoids have proven efficacy on clinical symptoms and structural damage, their side effects (hypertension, insulin resistance, weight gain, osteoporosis, fractures, infections, gastric ulcer, adrenal suppression) restrict their long-term use. Other treatments also have highly unfavorable safety profiles in the elderly: drug interactions, renal failure, cardiovascular events and gastrointestinal bleeding for NSAIDs; dependence, respiratory depression and confusion for narcotics [10]. The last ten years have seen profound changes in therapeutic management. On the one hand, new biotherapies, primarily TNF antagonists, have expanded the range of DMARDs. On the other hand, the goal of these treatments has evolved and is now based on achieving remission as rapidly as possible and preventing structural damage, in order to preserve function and quality of life over the long-term by means of regular adjustments of doses, drugs and combinations of DMARDs. This personalized, more aggressive strategy, known as "tight control," has greatly improved patient outcomes. Smolen et al. have recently proposed a new nomenclature that classifies older treatments such as methotrexate as Conventional Synthetic DMARDs (csDMARDs) as opposed to biotherapies, or "Biological Originator" (boDMARDs) [11].

Due to fear of infection or overly aggressive treatment, elderly patients are less likely than younger subjects to receive the newer therapies. In a large cohort of United States veterans with EORA (mean age: 63 years), methotrexate as first-line treatment increased from 39.9% to 57.2% and biologics from 3% to 6.7% between 1999–2001 and 2008–2009 [12]. Although the use of boDMARDs increased over time, they were less commonly used in older patients, with a 50% decrease after age 65 compared to patients below age 45 [12]. In a Medicare population in the United States (mean age: 70 years), the use of boDMARDs in RA increased from 4.7% in 2000 to 13.2% in 2006, as compared to 26% in a population 10 years younger [13]. In the North American CORRONA (Consortium of Rheumatology Researchers of North America) registry of RA patients, older patients received methotrexate as a single agent more often and at lower doses, with more frequent use of glucocorticoids, while biologics and combination DMARD therapy were used less frequently, despite comparable disease severity and activity [14]. These inequalities were also seen in the Dutch and Swedish registries, even though elderly patients often have more active disease [15]. These findings were further confirmed in the Swiss registry, which showed that glucocorticoids were used as first-line treatment in 68% of elderly patients versus 25.4% of younger patients, and that boDMARDs were less often used during follow-up (6.6% versus 14.1%) [6].

Obstacles to the use of biologic therapies are related not only to prescribers but also to patients. The two main reasons for resisting changes in RA therapy were fear of loss of disease control (OR 6.8) and fear of side effects (OR 4.4), reported by two-thirds of patients. Physician opinion on the current treatment (OR 1.9) and fear of high costs (OR 1.3) lagged far behind [16].

4. Effective treatments

The use of biotherapies is warranted by the elevated levels of inflammatory cytokines involved in the pathophysiology of many inflammatory diseases. In EORA, IL-6 levels are higher and TNF levels lower than in young subjects. Furthermore, in both age groups, a positive correlation has been found between IL-1, IL-6, TNF, IFN-γ (Interferon), IL-8 and the DAS28 score, and between IL-1 and TNF and joint erosions [17]. In the elderly population, high levels of IL-1ra and TNF were generally associated with an increased risk of death at one year [18].

Evidence for the benefits of biologic therapies in the elderly is scarce and mainly concerns the TNF antagonists in RA, which are slightly less efficacious than in young patients (Table 1). A randomized, controlled study showed that the benefit of adding etanercept to methotrexate for the treatment of RA, in terms of ACR (American College of Rheumatology) response and radiographic progression, was maintained in elderly population, albeit less marked, without statistically significant difference compared with subjects under age 65 [19,20]. Combination therapy with methotrexate plus infliximab or adalimumab resulted in a better clinical and radiologic response than methotrexate alone in RA patients, even in the oldest age category (70–80 years) [21]. In a Swiss registry, a smaller proportion of elderly patients achieved a good response to TNF antagonists, although improvements in DAS scores at 2 years were similar in patients above and below 65 years of age [22]. In the British Rheumatology Register, age had no effect on the response to anti-TNF therapy [23]. The DREAM (Dutch RhEumatology Arthritis Monitoring) registry confirmed that anti-TNF therapy decreased RA disease activity at 12 months across all age groups, although it