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Secukinumab retention rate is greater in patients with psoriatic arthritis presenting with axial involvement

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SUMMARY

Psoriatic arthritis (PsA) is an inflammatory disease characterized by peripheral and axial involvement. Biological disease-modifying antirheumatic drugs (bDMARDs) are the mainstream treatment for PsA and bDMARDs retention rate is a proxy for the drug's overall effectiveness. However, it is unclear whether IL-17 inhibitors can have a higher retention rate than tumor necrosis factor (TNF) inhibitors, in particular in axial or peripheral PsA.

A real-life observational study was conducted on bDMARD naïve PsA patients initiating TNF inhibitors or secukinumab. Time-to-switch analysis was carried out with Kaplan-Meyer curves (log-rank test) truncated at 3 years (1095 days). Sub-analyses of Kaplan-Meyer curves between patients presenting with prevalent peripheral PsA or prevalent axial PsA were also conducted. Cox regression models were employed to describe predictors of treatment switch/swap.

Data on 269 patients with PsA naïve to bDMARD starting either TNF inhibitors (n=220) or secukinumab (n=48) were retrieved. The overall treatment retention at 1 and 2 years was similar for secukinumab and TNF inhibitors (log-rank test p NS). We found a trend towards significance in the Kaplan-Meyer at 3 years in favor of secukinumab (log-rank test p 0.081). Predominant axial disease was significantly associated with a higher chance of drug survival in secukinumab users (adjusted hazard ratio 0.15, 95% confidence interval = 0.04-0.54) but not in TNF inhibitor users.

In this real-life, single-center, study on bDMARD naïve PsA patients, axial involvement was associated with longer survival of secukinumab but not of TNF inhibitors. Drug retention of secukinumab and TNF inhibitors were similar in predominantly peripheral PsA.

Key words: *Secukinumab, psoriatic arthritis, retention rate, tumor necrosis factor inhibitors, axial psoriatic arthritis, spondylarthritis.*

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease (1). Biologic therapies are recommended for the treatment of PsA in patients who respond inadequately to first-line treatment with non-steroidal anti-inflammatory drugs and/or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (1). Proinflammatory cytokine IL-17A mediates multiple biological functions in PsA, resulting in joint and entheseal inflammation and structural damage. Increased levels of IL-17-producing cells have been correlated with measures of disease activity, structural damage, and bone loss (2). Secukinumab selectively binds and neutralizes IL-17A. While in 2015, the European league against rheumatism stated that it was usual practice to start a tumor necrosis factor inhibitor (TNFi) in comparison with other biological disease-modifying antirheumatic drugs (bDMARDs), the last update of these recommendations did not distinguish anymore between TNFi, IL-12/23 inhibitors (IL-12/23i), and IL-17 inhibitors (1). Albeit many clinical trials and real-life studies have been published on the use of TNF inhibitors, few works have been published on IL-17 inhibitors, and the majority were randomized clinical trials (3).

The retention rate of a biological drug (percentage of patients remaining on treatment

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over time) provides an index of a drug's overall effectiveness. The main objective of the present study is to compare the real-life retention rate of secukinumab *vs* TNF inhibitors in bDMARD naïve axial and peripheral PsA.

MATERIALS AND METHODS

Data collection

We retrospectively analyzed prospectively collected data of patients with PsA starting bDMARDs at the outpatient service of the Rheumatology Unit of the University of Verona from January 2016 through January 2020. Patients were seen every 3-4 months as per clinical practice. Inclusion criteria were: i) patients with PsA according to the classification criteria for psoriatic arthritis; ii) age ≥18 years; iii) starting treatment with either secukinumab 150 mg or TNF inhibitors. Patients on secukinumab received a subcutaneous injection (150 mg) at weeks 0, 1, 2, 3, 4, and every 4 weeks thereafter following the manufacturer's instructions. Patients on TNF inhibitors received treatment according to the manufacturer's instructions at full dosage. The following clinical, radiological, and demographic parameters were collected: gender, age, weight, height, PsA characteristics at baseline (prevalent peripheral disease *vs* prevalent axial disease), disease activity in psoriatic arthritis (DAPSA) score, C-reactive protein serum concentrations, conventional radiographies of hands, feet and target joints of arthritis, magnetic resonance imaging (MRI) of lumbar spine and sacroiliac joints in patients with suspected axial disease, disease duration, systemic treatment with conventional and biological therapies including methotrexate, cyclosporine, leflunomide, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, and secukinumab. The disease subset at baseline (prevalent peripheral disease *vs* prevalent axial disease) was defined as follows. Axial disease: the presence of (i) inflammatory back pain for at least 6 weeks and (ii) bone marrow edema on MRI T2 weighted or short tau inversion recovery images on sacroiliac joints (at least 2 consecutive slices at the subchondral bone) or lumbar spine (at least 3 inflammatory lesions of the anterior and/or posterior corners).

Statistical analyses

Group comparisons were performed using a Student's t-test and Mann–Whitney U test (for normally and non-normally distributed continuous variables, respectively). The time-to-event analysis was performed with Kaplan-Meyer curves (log-rank test) truncated at 3 years (1095 days). We conducted sub-analyses of Kaplan-Meyer curves between patients with prevalent peripheral disease or prevalent axial disease. Patients were censored if the switch was due to adverse events or at the study end (3 years) or earlier if the follow-up was shorter. We also employed Cox regression models to describe predictors of treatment switch/swap. The variable included in the model were: age (continuous), gender (male *vs* female), body mass index (continuous), disease duration (continuous), concomitant treatment with cDMARDs (absent *vs* present), prevalent pattern (prevalent peripheral disease *vs* prevalent axial disease), erosive disease (deemed by an expert rheumatologist at baseline on plain X-ray of hands, feet and target joints), DAPSA score at baseline (continuous). Differences were considered significant at $p<0.05$.

All statistical analyses were performed using SPSS Version 26 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 9.3.1 (GraphPad Software, San Diego, CA, USA).

The study was conducted according to the protocol BIOREVE 534CESC approved by the University of Verona local Ethic Committee, in accordance with the 1964 Helsinki Declaration and its later amendments.

RESULTS

Baseline characteristics

A total of 305 patients with PsA starting bDMARDs were identified. Data on 269 patients with PsA naïve to bDMARD starting either TNF inhibitors (n=220) or secukinumab (n=48) were retrieved. Descriptive characteristics of the study population, stratified by treatment and prevalent pattern

Table I - Baseline characteristics of the cohort stratified by prevalent presenting patterns (axial or peripheral disease) and treatment (secukinumab or tumor necrosis factor inhibitors).

	Secukinumab (n=48)		Tumor necrosis factor inhibitors (n=220)	
	Peripheral predominant (n=28)	Axial predominant (n=20)	Peripheral predominant (n=132)	Axial predominant (n=88)
Age, years (±SD)	53.0 (10.5)	56.0 (12.1)	55.9 (11.8)*	52.5 (12.5)*
Sex, female (%)	15 (53.6)	10 (50.0)	65 (49.2)	53 (60.2)
Weight, kg (±SD)	72.5 (15.2)	70.6 (17.3)	73.6 (14.2)	72.7 (13.3)
Height, cm (±SD)	165 (16)	167 (18)	168 (13)	164 (14)
Disease duration, years (IQR)	4 (1-9)	3 (1-6)	5 (1-9)	5 (2-8)
Treatment with cDMARD, n. (%)	5 (17.9)*	0 (0)*	10 (7.6)	3 (3.4)
DAPSA score at baseline, n. (IQR)	31.7 (21.0-39.8)	24.5 (15.8-30.0)	22.2 (7.1-34.5)	17.9 (7.1-23.1)
Extra-articular disease, n. (%)	0 (0)*	5 (25.0)*	13 (9.8)*	17 (19.3)*
Erosive disease, n. (%)	21 (75.0)	12 (60.0)	62 (47.0)*	19 (21.6)*

SD, standard deviation; IQR, interquartile range; cDMARD, conventional disease-modifying anti-rheumatic drug; DAPSA, disease activity in psoriatic arthritis. *p<0.05.

at baseline are given in Table I. We did not find any significant difference between secukinumab users and TNF inhibitors users as regards baseline characteristics.

Among TNF users, 71 were treated with adalimumab 40 mg every 2 weeks (68 adalimumab biosimilar and 3 originator), 74 were treated with etanercept 50 mg every week (70 etanercept biosimilar and 4 originator), 50 were treated with golimumab 50 mg every 4 weeks, 14 were treated with certolizumab pegol 200 mg every 2 weeks and 11 were treated with infliximab 5 mg/kg every 8 weeks (11 infliximab biosimilar).

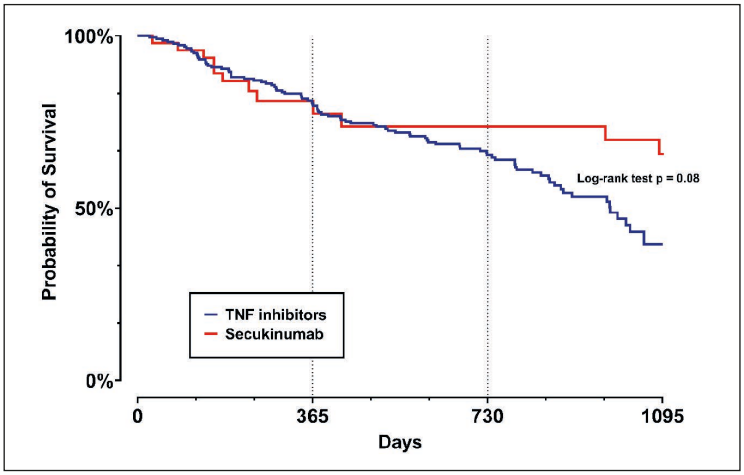

Figure 1 - Kaplan-Meyer curves for drug retention at 3 years for secukinumab and tumor necrosis factor inhibitors as first-line of treatment. *TNF, tumor necrosis factor.*

Treatment retention

The overall drug retention at 1 and 2 years was similar for secukinumab and TNF inhibitors (log-rank test p = NS). We found a trend towards significance in the Kaplan-Meyer curve at 3 years (log-rank test p = 0.081). In Figure 1 the Kaplan-Meyer curves for secukinumab and TNF inhibitors at 3 years of follow-up are depicted. Figure 2 shows the Kaplan-Meyer curves stratified by the prevalent pattern at baseline (axial disease *vs* peripheral disease). We found that patients with prevalent axial disease treated with secukinumab had greater drug retention compared to patients treated with TNF inhibitors (either with prevalent axial disease or prevalent peripheral disease) and to patients starting secukinumab with prevalent peripheral disease (log-rank test p = 0.02).

In the Cox regression model, the baseline DAPSA score was the only significant predictor of discontinuation at 3 years (β 0.020 SE 0.001, p = 0.02). We did not find any significant difference between secukinumab and TNF inhibitors. In sub-groups analysis stratified by starting treatment, we found that axial disease was significantly associated with longer secukinumab retention

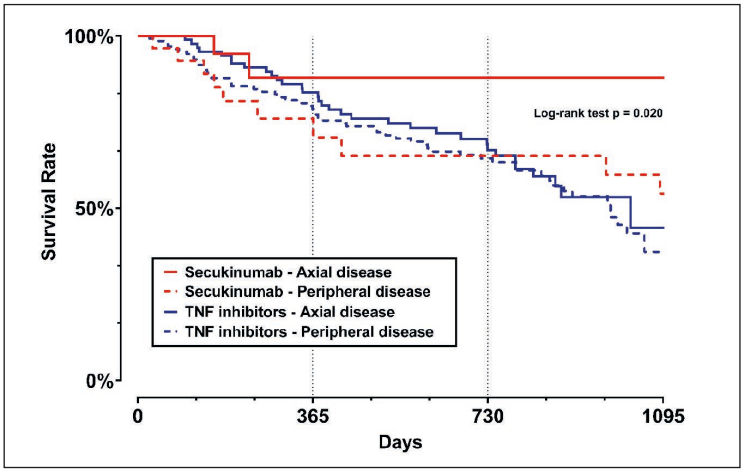

Figure 2
Kaplan-Meyer curves stratified by prevalent pattern at baseline. *TNF, tumor necrosis factor.*

Table II - Cox regression model for the prediction of switch/swap in patients initiating secukinumab.

Covariates	aHR (95% CI)	p value
Gender (female)	0.69 (0.28 to 1.69)	0.414
Age	0.99 (0.95 to 1.03)	0.754
BMI	1.2 (0.89 to 1.31)	0.330
Disease duration	0.98 (0.89 to 1.07)	0.639
Axial disease	0.15 (0.04 to 0.54)	0.004
DAPSA at baseline	0.98 (0.95 to 1.01)	0.375
Treatment with cDMARDs	0.53 (0.13 to 2.16)	0.374
Erosive disease at baseline	0.54 (0.17 to 1.67)	0.285

aHr, adjusted hazard ratio; CI, confidence interval; BMI, body mass index; DAPSA, disease activity in psoriatic arthritis; cDMARDs, conventional disease-modifying.nti-rheumatic drug.

(adjusted hazard ratio 0.15, 95% confidence interval 0.04-0.54). The Cox regression model for the prediction of switch/swap in secukinumab users is presented in Table II.

DISCUSSION AND CONCLUSIONS

Herein we conducted a real-life observational study on patients with PsA initiating secukinumab or TNF inhibitors as first-line bDMARD. Overall, we did not observe any significant difference in terms of retention rate between the two drugs. However, we found that patients with prevalent axial PsA treated with secukinumab had higher drug retention compared to patients with peripheral PsA treated with either TNF inhibitors or secukinumab. Axial involvement was a significant and independent predictor of a longer retention rate in bDMARD naïve patients starting secukinumab.

To the best of our knowledge, no other studies have been conducted with this aim. Nonetheless, consistent with our finding, secukinumab was shown to outperform TNF inhibitors in real-life studies on bDMARD naïve patients with ankylosing spondylitis in terms of both effectiveness and radiographic response (3-9).

A possible explanation for such a finding might reside in the peculiar metabolic signature of PsA with axial involvement (10). Patients with axial involvement have significantly lower levels of circulating Dkk1 (11-13), a Wnt inhibitor that has been inversely associated with the radiographic progression of PsA (11). Interestingly, IL-

17 blockade had been shown to determine a quick increase in Dkk1 serum levels whereas TNF inhibitors reduced Dkk1 levels in the short term (14-16). This difference might indeed explain the greater efficacy of IL-17 inhibitors on radiological progression at the axial skeleton. Ramonda *et al*. reported that gender, body mass index, and dosage of secukinumab were factors associated with a higher chance of discontinuation at 24 months (17). However, these authors did not include axial involvement in the Cox regression analysis, making comparisons with our study unfeasible. Nevertheless, the treatment retention rate for secukinumab was comparable at 24 months. Interestingly, both Ramonda *et al.* and Alonso *et al.* found that male gender was protective against treatment discontinuation (17, 18). Of note, it is well known that male sex confers a greater risk of axial involvement in PsA (19). The female sex may constitute a predisposing risk factor for discontinuation and therapeutic switches. Female PsA patients more frequently present a polyarticular and entheseal pattern, often compounded by fibromyalgia, which amplifies the perception of pain and fatigue (20, 21).
Our study should be interpreted considering its strengths and limitations. The greatest strength of the study was the long-term follow-up and the selection of bDMARDs naïve patients. In addition, we included in the analysis only patients with treatment discontinuation due to primary or secondary inefficacy, excluding all subjects that withdrew the drug for adverse events. We had access to radiological data to determine the erosive status and/or axial involvement at baseline. However, given the real-life, not-randomized, observational nature of the study, we cannot rule out some sort of channeling bias. Indeed, rheumatologists might have been more inclined to prescribe secukinumab in patients with axial PsA. Nonetheless, the proportion of patients with axial PsA that initiated secukinumab was not significantly different from those who initiated TNF inhibitors. In addition, we did not have access to several clinical characteristics that might have impacted the drug's retention rate in favor of one mechanism of action. For example, we did not have access to comorbidities (or proxy for comorbidity status such as the Charlson comorbidity index) and psoriasis severity score. The latter has been indeed found to be associated with greater survival of secukinumab (22). However, none of the patients was treated with secukinumab 300 mg, possibly reflecting a population with only mild psoriasis.
In conclusion, we found similar drug retention for secukinumab and TNF inhibitors in PsA. However, the secukinumab retention rate was higher in patients with prevalent axial PsA. From our results, we might suggest that PsA patients with axial involvement might benefit more from starting secukinumab as compared to TNF inhibitors.

Contributions
GA, conceptualization, formal analysis; GA, LI, data curation; GA, LI, CB, EF, AC, OV, DG, MR, AF, investigation, writing – review, editing; MR, project administration, supervision; GA, MR, validation; GA, CB, writing – original draft.

Conflict of interest
GA, declares personal fees from Theramex and Galapagos; LI, declares personal fees from AbbVie, Amgen, Biogen, Merck Sharp & Dohme, Eli Lilly, Novartis, Celgene, Sandoz, Janssen, and UCB; AC, declares personal fees from Abbvie, Janssen, Cilag and Novartis; DG, declares personal fees from Amgen, Eli-Lilly, Merck Sharp & Dohme, Organon; MR, served as a consultant or speaker for Abbvie, Amgen, Bms, Eli Lilly, Galapagos, Menarini, Novartis, Pfizer, Sandoz, Theramex, Ucb. All other authors declare no conflict of interest. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no conflicts of interest related to the present paper.

Ethics approval and consent to participate
The study was conducted according to the protocol BIOREVE 534CESC approved by the Ethics Committee of the University of

Verona Hospital, in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Patient and public involvement statement
This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Transparency declaration
The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Availability of data and materials
Data and materials are available by the authors. No additional data are available.

REFERENCES

1. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020; 79: 700-12.
2. Jandus C, Bioley G, Rivals J-P, Dudler J, Speiser D, Romero P. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheum. 2008; 58: 2307-17.
3. Baraliakos X, Gossec L, Pournara E, Jeka S, Mera-Varela A, D'Angelo S, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial. Ann Rheum Dis. 2021; 80: 582-90.
4. Purmonen T, Puolakka K, Mishra D, Gunda P, Martikainen J. Cost-effectiveness of secukinumab compared to other biologics in the treatment of ankylosing spondylitis in Finland. Clinicoecon Outcomes Res. 2019; 11: 159-68.
5. Emery P, Van Keep M, Beard S, Graham C, Miles L, Jugl SM, et al. Cost effectiveness of secukinumab for the treatment of active ankylosing spondylitis in the UK. Pharmacoeconomics. 2018; 36: 1015-27.
6. Goeree R, Chiva-Razavi S, Gunda P, Jain M, Jugl SM. Cost-effectiveness analysis of secukinumab in ankylosing spondylitis from the Canadian perspective. J Med Econ. 2019; 22: 45-52.
7. Mease PJ, Landewé R, Rahman P, Tahir H, Singhal A, Boettcher E, et al. Secukinumab provides sustained improvement in signs and symptoms and low radiographic progression in patients with psoriatic arthritis: 2-year (end-of-study) results from the FUTURE 5 study. RMD Open. 2021; 7: e001600.
8. Baraliakos X, Gensler LS, D'Angelo S, Iannone F, Favalli EG, de Peyrecave N, et al. Biologic therapy and spinal radiographic progression in patients with axial spondyloarthritis: a structured literature review. Ther Adv Musculoskelet Dis. 2020; 12: 1759720X20906040.
9. Karmacharya P, Duarte-Garcia A, Dubreuil M, Murad MH, Shahukhal R, Shrestha P et al. Effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis. Arthritis Rheumatol. 2020; 72: 733-49.
10. Adami G. Regulation of bone mass in inflammatory diseases. Best Pract Res Clin Endocrinol Metab. 2021; 36: 101611.
11. Fassio A, Idolazzi L, Viapiana O, Benini C, Vantaggiato E, Bertoldo F, et al. In psoriatic arthritis Dkk-1 and PTH are lower than in rheumatoid arthritis and healthy controls. Clin Rheumatol. 2017; 36: 2377-81.
12. Orsolini O, Adami G, Rossini M, Ghellere F, Caimmi C, Fassio A, et al. Parathyroid hormone is a determinant of serum Dickkopf-1 levels in ankylosing spondylitis. Clin Rheumatol. 2018; 37: 3093-8.
13. Rossini M, Viapiana O, Idolazzi L, Ghellere F, Fracassi E, Troplini S, et al. Higher level of Dickkopf-1 is associated with Low bone mineral density and higher prevalence of vertebral fractures in patients with ankylosing spondylitis. Calcif Tissue Int. 2016; 98: 438-45.
14. Adami G, Orsolini G, Adami S, Viapiana O, Idolazzi L, Gatti D, et al. Effects of TNF inhibitors on Parathyroid hormone and wnt signaling antagonists in rheumatoid arthritis. Calcif Tissue Int. 2016; 99: 360-4.
15. Orsolini G, Adami G, Adami S, Viapiana O, Idolazzi L, Gatti D, et al. Short-term effects of TNF inhibitors on bone turnover markers and bone mineral density in rheumatoid arthritis. Calcif Tissue Int. 2016; 98: 580-5.
16. Fassio A, Adami G, Gatti D, Orsolini G, Giollo A, Idolazzi L, et al. Inhibition of tumor necrosis factor-alpha (TNF-alpha) in patients with early rheumatoid arthritis results in acute

changes of bone modulators. Int Immunopharmacol. 2018; 67: 487-9.
17. Ramonda R, Lorenzin M, Carriero A, Chimenti MS, Scarpa R, Marchesoni A, et al. Effectiveness and safety of secukinumab in 608 patients with psoriatic arthritis in real life: a 24-month prospective, multicentre study. RMD Open. 2021; 7: e001519.
18. Alonso S, Villa I, Fernández S, Martín JL, Charca L, Pino M, et al. Multicenter study of secukinumab survival and safety in spondyloarthritis and psoriatic arthritis: secukinumab in Cantabria and ASTURias study. Front Med (Lausanne). 2021; 8: 679009.
19. Diaz P, Feld J, Eshed I, Eder L. Characterising axial psoriatic arthritis: correlation between whole spine MRI abnormalities and clinical, laboratory and radiographic findings. RMD Open. 2022; 8: e002011.
20. Costa L, Perricone C, Chimenti MS, Del Puente A, Caso P, Peluso R, et al. Switching between biological treatments in psoriatic arthritis: a review of the evidence. Drugs R D. 2017; 17: 509-22.
21. Lorenzin M, Ortolan A, Cozzi G, Calligaro A, Favaro M, Del Ross T, et al. Predictive factors for switching in patients with psoriatic arthritis undergoing anti-TNFα, anti-IL12/23, or anti-IL17 drugs: a 15-year monocentric real-life study. Clin Rheumatol. 2021; 40: 4569-80.
22. Ortolan A, Lorenzin M, Leo G, Pampaloni F, Messina F, Doria A, et al. Secukinumab drug survival in psoriasis and psoriatic arthritis patients: a 24-month real-life study. Dermatology. 2022; 238: 897-903.