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The effects of iguratimod combined with methotrexate and hydroxychloroquine on bone mineral density in patients with rheumatoid arthritis

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In this study, we aimed to explore the effects of iguratimod (IGU) combined with methotrexate (MTX) and hydroxychloroquine (HCQ) on bone mineral density (BMD) in patients with rheumatoid arthritis (RA). 76 patients who received IGU combined with MTX and HCQ were included in this retrospective study. After 48 weeks treatment of IGU combined with MTX and HCQ, the BMD at the L1-L4 (p<0.01), left femoral neck (p<0.01) and left total hip (p<0.01) were significantly increased. Especially, the BMD at left femoral neck was significantly increased from baseline to week 24 (p<0.05). With regard to inflammatory reaction, there were statistically significant reductions in the RF (p<0.05), CRP (p<0.05), ESR (p<0.01), anti-CCP (p<0.01) from baseline to week 48. The most common adverse events were gastrointestinal reaction and transaminase elevation. The combination of IGU, MTX and HCQ could significantly improve the BMD and restrain inflammatory reaction. No additional adverse events were noticed in our research. This study provides valuable information for treatment of osteopenia in patients with RA.

1. Introduction

Rheumatoid arthritis (RA) is a common inflammatory, chronic disease of joint with systemic autoimmune basis (Abbasi et al. 2019). In China, the prevalence of RA is reported to be 0.42%, affecting more than 5 million patients in 2013 (Jin et al. 2017). RA primarily affects the lining of the synovial joints, which characterized by joint damage, chronic joint inflammation, and bone erosion with osteoclast activation. The lesions can lead to impaired movement and disability (Chaudhari et al. 2016; Guo et al. 2018). It has been reported that in some patients with RA, bone erosion occurs at an early stage of RA which can lead to massive bone loss and articular cartilage lesions. Among 405 patients with RA, 370 patients showed low bone mass (Iwata et al. 2016). Notably, without early intervention, low bone mass is highly likely to develop into osteoporosis which can cause vertebral fractures. Thus, early intervention is significant for patients with RA.

As a novel disease-modifying antirheumatic drug, iguratimod (IGU) can effectively inhibit the expression of various inflammation factors, and B cells producing immunoglobulins and autoantibodies (Suto et al. 2019). In addition, IGU has osteoprotective effects such as promoting bone formation and inhibiting bone resorption (Xie et al. 2020). A study has demonstrated that IGU plays an important role in restraining osteoclast precursor cell lines differentiated into osteoclasts in rats (De Grooth et al. 1994). Furthermore, in the ST2 cell line, IGU stimulates ST cells to secrete osteocalcin (Zhao et al. 2019). At the molecular level, IGU suppressed the peroxisome proliferator activated receptor γ/c Fos pathway, which is essential in RANKL induced osteoclast differentiation (Wu et al. 2017). These results suggest the application of IGU as a unique treatment method in prevention of bone loss. However, there are few clinical studies regarding IGU on bone loss. In the present study, we aimed to explore the effects of IGU combined with MTX and HCQ on osteoprotective and inflammatory reaction in patients with RA to provide valuable information for treatment of patients with RA.

List of abbreviations:
IGU, iguratimod; MTX, methotrexate; HCQ, hydroxychloroquine; BMD, bone mineral density; RA, rheumatoid arthritis; ACR, American College of Rheumatology; RF, rheumatoid factor; CRP, C-Reactive Protein; ESR, erythrocyte sedimentation rate; anti-CCP, anti-cyclic citrullinated peptide antibody; ASO, antistreptolysin O; IgG, immunoglobulin G; IgA, immunoglobulin A; C3, complement component 3; IQR, interquartile range.

2. Investigations and results

2.1. Baseline characteristics

The baseline characteristics of included patients were showed in Table 1. A total of 76 patients with RA were included in this study. There were 2 (2.6%) males and 74 (97.4%) females, with a median age of 59.05±10.95 years. The mean disease duration of patients was 11.84±7.03 years.

Table 1: Baseline characteristics

Characteristics	N=76
Gender (n, %)	
Male	2 (2.63%)
Female	74 (97.37%)
Age (years), mean±SD	59.05±10.95
Disease duration (years), mean±SD	11.84±7.03

Table 2: Changes of BMD after treatment

Sites	Baseline	Week 24	Week 48
L1-L4 (g/cm^3), Median (Q1,Q3)	-1.55 (-2.3,-0.6)	-1.5 (-2.5,-0.4)	-1.35 (-2.5,-0.4)$^{**,\#\#}$
Left femoral neck (g/cm^3), mean±SD	-1.72 (1.08)	-1.62 (1.10)*	-1.45 (1.03) $^{**,\#\#}$
Left total hip (g/cm^3), mean±SD	-1.62 (1.12)	-1.60 (1.08)	-1.46 (1.04) $^{**,\#\#}$

BMD, bone mineral density; L1-L4, lumbar spine 1-4; * vs. baseline, p<0.05; ** vs. baseline, p<0.01; $^{\#\#}$ vs. week 24, p<0.01

2.2. BMD

As shown in Table 2, there were statistically significant increases in BMD at the L1-L4 (from -1.55 to -1.35 g/cm^3, p<0.01), left femoral neck (from -1.72 to -1.45 g/cm^3, p<0.01) and left total hip (from -1.62 to -1.46 g/cm^3, p<0.01) from baseline to week 48. Especially, from baseline to week 24, the BMD at left femoral neck increased from-1.72 to -1.62 g/cm^3 (p<0.05). We further compared the changes of BMD at the three sites among different time points. There were statistically significant increases in BMD at the L1-L4 (from -1.5 to -1.35 g/cm^3, p<0.01), left femoral neck (from -1.62 to -1.45 g/cm^3, p<0.01) and left total hip (from -1.60 to -1.46 g/cm^3, p<0.01) from week 24 to week 48.

2.3. Inflammatory indicator

As shown in Table 3, there were statistically significant reductions in the RF (from 27.3 to 20 IU/ml, p<0.05), CRP (from 3.45 to 2.85 μg/L, p<0.05), ESR (from 34 to 23.5 mm/h, p<0.01), anti-CCP (from 103.95 to 75.25 μg/L, p<0.01) from baseline to week 48. Remarkably, after 12 weeks of combination drug therapy, ESR (from 34 to 23 mm/h, p<0.01) and C3 (from 0.90 to 0.83 g/L, p<0.05) were significantly decreased compared to baseline. In addition, compared to baseline, anti-CCP was increased from 103.95 to 154.55 μg/L (p<0.01) at week 12. No significant differences in IgG, IgA, IgM and C4 were observed after combination drug therapy for 48 weeks (Table 4).

2.4. Safety analysis

After combination drug therapy, no statistic differences were observed in blood routine examination, kidney and liver function compared to baseline. Throughout RA treatment, the most common adverse events were gastrointestinal reactions and transaminase elevation. No adverse events such as hyperglycemia and severe respiratory tract infection occurred.

3. Discussion

RA is the most commonly diagnosed systemic inflammatory arthritis that affects approximately 1% of the world population (Wasserman 2011). Approximately 15 to 36% of patients with RA suffer osteoporosis as a complication as early as 2 years after disease onset, increasing the risk of decreased bone density and increased fracture risk (Haugeberg et al. 2000). MTX is a potent disease-modifying antirheumatic drug and preferred treatment for RA (Xie et al. 2019). HCQ is widely used in the treatment of autoimmune disease, such as RA. MTX combined with HCQ is a common therapeutic regimen for patients with RA. IGU is a novel DMARD which adjust bone metabolism by stimulating osteoblastic differentiation and inhibiting osteoclastogenesis. The studies on the treatment of RA with the above three drugs alone or in combination have been reported. However, there are few studies on the efficacy of IGU combined with MTX and HCQ on osteopenia in patients with RA. In this study, we investigated whether the combination of the above three drugs can improve osteopenia in in patients with RA.

A clinical research of over five years, showed no adverse effects of low-dose (10 mg/week) MTX on bone density in patients with RA (Liu et al. 2015). Furthermore, administration of long-term, low-dose MTX can cause severe osteopenia in female rats by reducing osteoblast function and increasing bone resorption (May et al. 1996). Other recently research showed that BMD in the MTX

Table 3: Changes of major inflammatory indicators

Inflammatory indicator	Baseline	Week 12	Week 24	Week 36	Week 48
RF (IU/mL), median (Q1,Q3)	27.3 (20.0, 97.6)	23.75 (20.0, 99.7)	20.95 (20.0, 108.0)	22.95 (20.0, 99.0)	20 (20.0, 79.1)$^{*,\Delta}$
CRP (μg/L), median (Q1,Q3)	3.45 (1: 9, 19.5)	4.7 (2.5, 12)	2.8 (1.8,10.0)**	3.2 (1.5, 10.1)$^{+}$	2.85 (1.59, 10.6)$^{*,++}$
ESR (mm/h), median (Q1,Q3)	34 (10.0, 49)	23 (13, 43)**	24 (8.0, 41.0)**	22.5 (10.0, 52.0)	23.5 (12.0, 37.0)**
Anti-CCP (μg/L), median (Q1,Q3)	103.95 (21.1, 651.1)	154.55 (17.6, 741.3)**	114.15 (16.7, 454.1)$^{**,++}$	91.35 (14.2, 409.1)$^{**,++,\#\#}$	75.25 (9.6, 69.3)$^{**,++,\#\#,\Delta\Delta}$
C3 (g/L), mean±SD	0.90±0.22	0.83±0.18*	0.83±0.19	0.87±0.23	0.89±0.20$^{+,\#\#}$
ASO (U/mL), median (Q1,Q3)	34.9 (25.0, 60.1)	34.6 (25.0, 60.5)	36.55 (25.0, 57.7)	34.8 (25.0, 54.7)	35.15 (25, 55.2)**

RF, inflammatory indicator including rheumatoid factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; anti-CCP, anti-cyclic citrullinated peptide antibody; C3, complement component 3; ASO, antistreptolysin O; * vs. baseline, p<0.05; ** vs. baseline, p<0.01; $^{+}$ vs. week 12, p<0.05; $^{++}$ vs. week 12, p<0.01; $^{\#\#}$ vs. week 24, p<0.01; $^{\Delta}$ vs. week 36, p<0.05; $^{\Delta\Delta}$ vs. week 36, p<0.01

Table 4: Changes of IgG, IgA, IgM and C4 after treatment

Indicator	Baseline	Week 12	Week 24	Week 36	Week 48
IgG (mg/mL), geometric mean±SD	13.09±1.32	12.91±1.32	13.01±1.31	13.00±1.26	13.01±1.26
IgA (mg/mL), geometric mean±SD	2.3±1.66	2.33±1.61	2.27±1.61	2.31±1.60	2.33±1.62
IgM (mg/mL), geometric mean±SD	1.16±1.73	1.17±1.66	1.17±1.74	1.20±1.67	1.22±1.55
C4 (g/L), mean±SD	0.19±0.06	0.19±0.06	0.19±0.06	0.19±0.07	0.20±0.06

IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C4, complement component 4

group significantly decreased by 6.9% compared to the control group (Liu et al. 2015). As a small molecular drug, IGU has been proven to have osteoprotective effect for treatment of RA patients. The conducted research showed that the combination of IGU with MTX is synergistic in patients with RA (Xia et al. 2016). In addition, other research found during treatment of RA with modifying-anti-rheumatic drugs in combination with low-dose prednisolone, that the BMD of femoral neck decreased non-significantly by 4.24% (Heidari et al. 2012). Notably, different from previous data, this study found that the combination of IGU, MTX and HCQ can effectively improve the BMD of patients with RA. After 48 weeks of combination drug therapy, the BMD at L1-L4, left femoral neck and left total hip were significantly increased. Moreover, the BMD at left femoral neck was significantly increased as early as week 24 of treatment. In a word, IGU combined with MTX and HCQ had significant effects on improving BMD in patients with RA.

In accordance with previous studies, we hypothesized that the mechanism of combination drug therapy improves BMD. First, combination drug therapy may suppress osteoclastogenesis by interfering with RANKL and TNF-α signal (Li et al. 2021). Second, combination drug therapy affects osteoclastogenesis and/or bone resorption causing decreased bone turnover resulting in net less bone loss (Both et al. 2018). Third, combination drug therapy reversed the degree of MTX in inhibiting bone growth and increasing bone resorption.

Inflammation is the most determinant of bone loss in patients with RA. Pharmacological studies have shown that various inflammatory cytokines, including interleukin (IL)-1, IL-6, and immunoglobulin can be inhibited by IGU (Jiang et al. 2020). However, in this study, the level of IgG, IgA, IgM and C4 were not be decreased by combination drug therapy. A previous study suggested that the average of ESR and CRP decreased significantly in MTX plus IGU group after 17 weeks of treatment (Xia et al. 2016). Furthermore, after 52 weeks combination drug therapy of IGU and MTX, ESR, and DAS28-C-reactive protein are all significantly decreased (Okamura et al. 2015). In this study, we investigated the effect of combination of IGU, MTX and HCQ in inflammatory reaction. In line with data from previously published study, we found the levels of C3, RF, CRP, ESR and anti-CCP significantly decreased by combination drug therapy. From baseline to week 12, the level of CRP was increased from 3.45 to 4.7μg/L. Then there was a significant decrease. We think that the reason for the above results may be that the 12-week treatment period is relatively short and the effect is not stable.

IGU alone or in combination with other drugs has a good safety profile (Hara et al. 2014). Another study clarified that the combination of IGU with MTX does not significantly increase the number of adverse events (Xia et al. 2016). A retrospective study found that IGU combined with MTX can cause upper digestive disorders (Fleischmann et al. 2017; van der Heijde et al. 2019). Low-dose GCs combined with MTX and HCQ significantly improves clinical outcomes, without enhancing adverse reactions (Hua et al. 2020). In this study, the most common adverse events were gastrointestinal reactions and transaminase elevation. In addition, no side effects such as hyperglycemia and severe respiratory tract infection were noticed in our research. This study suggested that combination of IGU with MTX and HCQ for RA appeared to be well tolerated.

Despite the important findings of this study, it still has limitations. First, after 48 weeks of combination drug therapy, there were no significant changes in the immune globulins, which may be caused by small-scale sample and short duration of medication. Second, this was a single-arm study, the methodological limitations may prevent it from obtaining the high level of reliability. Third, we do not verify the relationship between BMD and inflammatory reaction. Randomized controlled trials with large-scale samples and long-term follow up are needed to further verify the result and clarify the correlation between BMD and inflammatory reaction.

In conclusion, the combination of IGU, MTX and HCQ could significantly improve the BMD and restrain inflammatory reaction without additional adverse events. This study provides valuable information for treatment of osteopenia in patients with RA.

4. Experimental

4.1. Patients

A total of 76 patients with RA admitted to the Zhejiang Provincial People's Hospital from October 2018 to October 2020 were included in this retrospective study. This study was approved by the ethics committee of Zhejiang Provincial People's Hospital (2020QT321). All patients provided written informed consent.

Eligible patients were aged 18-85 years and diagnosed with RA based on the 1987 American College of Rheumatology (ACR) criteria or the 2010 EULAR/ACR classification criteria (Cader et al. 2011). All patients did not receive vitamin D or calcium for four months before treatment initiation, or bisphosphonates at least for one year before treatment initiation.

The exclusion criteria were as follows: I) patients received long-term treatment with glucocorticoids; II) patients had other autoimmune diseases; III) patients had disease which would affect bone metabolism; IV) patients had severe osteoporosis or pathological fractures; V) patients suffered from severe digestive system disease, liver disease, kidney disease, malignant tumor and other diseases.

4.2. Drug therapy

All patients received IGU combined with MTX and HCQ for 48 weeks. IGU was administered at the recommended dose of 25 mg twice a day (H20110084, Xiansheng, Jiangsu). MTX was administered at 10 mg once a week (H19983205, Zhengqing, Hunan). The dose of HCQ was 200 mg twice a day (H19990263, Shangyaozhongxizhiyao, Shanghai).

4.3. Outcomes assessment

Bone mineral density (BMD) was measured using a Dual Energy X-Ray Absorptiometry (USA) for lumbar spine (L1–L4), left femoral neck and left total hip at baseline, week 24 and 48.

Inflammatory indicators including rheumatoid factor (RF), C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide antibody (anti-CCP), antistreptolysin O (ASO), immunoglobulin G (IgG), IgA, IgM, complement component 3 (C3) and C4 were evaluated at baseline, week 12, 24, 36 and 48. ESR was detected by spectrophotometry. RF, CRP, ASO, IgG, IgA, IgM, C3 and C4 were measured by rate scattering turbidity test. Anti-CCP was evaluated by enzyme linked immunosorbent assay method. Security index, such as blood routine examination, liver function, renal function, etc. were tested at baseline, week 12, 24, 36 and 48.

4.4. Statistical analysis

All statistical analyses were performed by using SPSS version 20.0 (SPSS Institute. IL.USA). Normally distributed data (left femoral neck, left total hip, C3, C4) were expressed as mean±standard deviation (SD); log-normal distributed data (IgG, IgA and IgM) were expressed as geometric mean±SD, non-normally distributed data (L1-L4, RF, CRP, ESR, anti-CCP, ASO) were present as median (interquartile range [IQR]). Statistical significances between normally distributed data at different time points were determined with One-way Repeated Measures ANOVA followed by Bonferroni correction. Statistical significance was set at $p<0.05$.

4.5. Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Committee of Zhejiang Provincial People's Hospital (2020QT321). All participants signed an approved informed-consent form.

Conflicts of interest: The authors declare that they have no conflict of interest.

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